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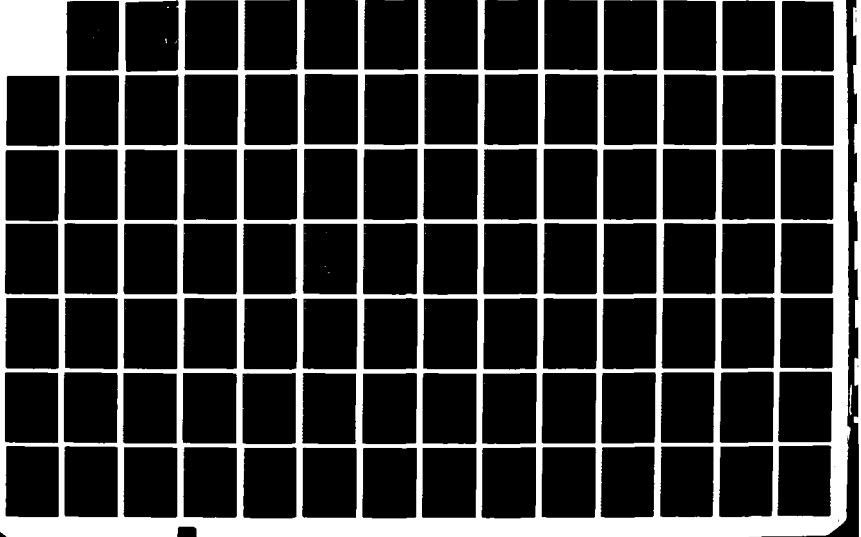

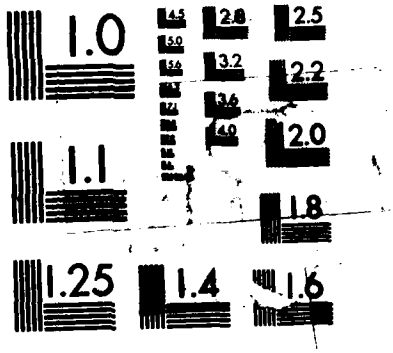

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CHRONIC MAMMALIAN TOXICOLOGICAL EFFECTS OF LAP WASTEWATER

Final Report

by

Janice M. Brown, Ted A. Jorgenson, and Ronald J. Spanggord

June 1983

Supported by

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2,4,6-trinitrotoluene (TNT); 1,3,5-trinitrohexahydro-1,3,5-triazine (RDX); LAP (load, assumble, and pack).

20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

The objective of these studies was to provide a comprehensive definition of the long-term toxicological effects of LAP wastewater (TNT/RDX in a ratio of 1.6 to 1) on Fischer-344 rats with respect to possible lesions at the biochemical and cellular levels. Acute oral LD50 values were determined to be 294 mg/kg for males and 325 mg/kg for the females. Based on the results of this study and a 14-day range-finding study, dietary levels of 12.5, 50, and 200 mg/kg/day were selected for use in the chronic study. Each treatment group contained 70 male and 70 female rats; the vehicle control group

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contained 75 rats of each sex. Because an excessive number of males receiving 200 mg/kg/day of LAP exhibited convulsions and death, the high-dose level was reduced to 100 mg/kg/day for both sexes after 12 weeks on test. However, aggressive behavior, convulsions, and death continued to occur, particularly in the males, and the entire dose level (consisting of 19 male and 69 female survivors) was terminated after 33 weeks on test. Males at the mid-dose level showed an increase in mortality compared with controls at 104 weeks (study termination); these rats also exhibited convulsions and aggressive behavior. Low-dose males and females at both the low- and mid-dose levels showed little response with regard to behavioral or clinical abnormalities, food consumption, and mortality; however, body weights in these groups were significantly decreased throughout the study.

Effects on both the myelocytic and erythrocytic series were seen in both sexes at the mid-dose level. Clinical chemistry parameters were affected to some degree in females at the low- and mid-dose levels; a dose response was seen in glucose, uric acid, K^+, triglycerides, LDH, total iron, A/G ratio, Na^+, CO_2, and biluribin. Only LDH was significantly decreased in males at both levels.

Treatment-related changes in relative organ weights consisted of an increase in liver weight in all treated groups, possibly reflecting an induction of hepatic enzymes to metabolize LAP, and an increase in kidney weight in males at all dose levels, reflecting kidney damage. The principal LAP-induced lesions observed as histopathological examination were degenerative changes in the eye and urinary system and decreased cellularity of the lymphoid tissues. These changes were generally restricted to the mid- and high-dose groups and were usually more pronounced in the males.

EXECUTIVE SUMMARY

Confirmatory oral LD50 and 14-day range-finding feeding studies on LAP were conducted with Fischer-344 rats. The results of these studies were used to establish dose levels for the chronic phase of this program, the objective of which was to provide a comprehensive definition of the long-term toxicological effects of LAP with respect to possible lesions at the biochemical and cellular levels.

In the LD50 study, six dose levels of LAP were tested with ten males and ten females at each level. The results of this study showed the single-dose oral LD50 to be 294 and 325 mg/kg for male and female Fischer-344 rats, respectively.

For the 14-day range-finding and chronic studies, LAP was incorporated into the diet by dissolving the compound in acetone, roto-evaporating the acetone, and adding 3% corn oil to the extract. In the 14-day range-finding study, five concentrations of LAP in the diet were tested with ten animals of each sex at each level. Consistently reduced food consumption and body weight gain were seen at the 0.5 and 0.7% dietary levels for both sexes; mortality also occurred at both levels. Occasionally, food consumption, body weights, gross behavior, and hematological parameters were adversely affected at the 0.3% level, but they were rarely affected at the 0.1 and 0.05% levels.

Based on the data from the 14-day range-finding study, dietary levels equivalent to dose levels of 12.5, 50, and 200 mg/kg/day were selected for the chronic study.

In the chronic study, each treatment group contained 70 rats of each sex. The vehicle control group consisted of 75 rats of each sex that received a 3% corn oil/roto-evaporated acetone/feed mixture in which the original acetone content was equal to that used to dissolve the LAP at the highest treatment level. After just one week on test, food consumption and body weights were reduced at the mid- (50 mg/kg/day) and high- (200 mg/kg/day) dose levels. During the first 12 weeks of the study, the high-dose males had severe convulsions that resulted in multiple abrasions and 10% of the rats had died by Week 12. Therefore, the high-dose level was reduced by 50% at that time. Body weights in the females and food consumption in both sexes began to increase and eventually exceeded control values. Convulsions and abnormal aggression continued to occur in both sexes, as did mortality in the males. After 33 weeks on test, all survivors in the high-dose groups were terminated. At the mid-dose level, convulsions and abnormal aggression were also exhibited, with the males being more severely affected. Mortality was significantly increased in

these males. Rats in the low-dose groups (12.5 mg/kg/day) showed no physiological or behavioral abnormalities and little response with regard to food consumption; body weights, however, were significantly decreased.

Results of the hematology analyses indicated that LAP had an effect on both the myelocytic and erythrocytic series of both sexes at the mid-dose level, although clinical chemistry parameters did not reflect the degree of kidney damage seen histologically in the mid-dose males. In the low-dose males, only LDH was significantly decreased. In the females, numerous changes in clinical chemistry parameters were seen, beginning at the low-dose level. Parameters significantly decreased included glucose, uric acid, K^+, triglycerides, LDH, total iron, and the A/G ratio; Na^+, CO_2, and total bilirubin were significantly increased at this level compared with controls.

Among the treatment-related changes in relative organ weights were an increase in liver weight in all treated groups, possibly reflecting an induction of hepatic enzymes to metabolize LAP, and an increase in kidney weight in the treated males, reflecting kidney damage.

The principal biologically significant LAP-induced toxic lesions observed at histopathological examination were degenerative changes in the eye and urinary system and decreased cellularity of the lymphoid tissue. These changes were generally restricted to the mid- and high-dose groups and were usually more pronounced in the males.

From the results of these studies, the ambient water quality criterion for protection of human health from ingestion of LAP through water or contaminated aquatic organisms was determined to be 4.26 mg/L.

QUALITY ASSURANCE UNIT

Final Report Statement

SRI International assures the quality and integrity of this project, which includes an acute oral LD_{50} study, a 14-day range finding feeding study, and a two-year chronic study for the U.S. Army Medical Research and Development Command researching the effects of the test compound, LAP wastewater, in rats. Dose levels for the two-year chronic toxicology study were established based on the results of the LD_{50} and 14-day studies. The two-year study was undertaken to determine long-term effects on rats.

A table representing the experimental phases inspected and inspection dates immediately follow. The raw data audit was completed on January 24, 1983 and the draft final report audit was completed on January 26, 1983. The results of these audits were communicated to the Study Director and SRI management on January 27, 1983.

The final report accurately describes the methods and standard operating procedures and reflects the raw data of the study. Any deviations from the approved protocol and standard operating procedures were made with proper authorization and documentation. The draft final report and final report were audited and reviewed on January 26, and July 22, 1983, respectively. The results of the draft and final report reviews were communicated to the Study Director and SRI management on January 27 and July 22, 1983, respectively.

Sherry J. Hansen

Quality Assurance Director

July 22, 1983

Date

Quality Assurance Unit
Final Report Statement
(continued)

Q A Inspection Schedule

Experimental Phase	Date Inspected	Date communicated to the Study Director and SRI Management
Blood chemistries & terminal necropsy	Feb. 25, 1982	Mar. 1, 1982
Terminal necropsy	Feb. 17, 1982	Feb. 17, 1982
Cage/feeder change, animal weight, clinical observations	Dec. 17, 1981	Dec. 18, 1981
Histology	Dec. 7, 1981	Dec. 9, 1981
Cage/feeder change, animal weight, clinical observations	Aug. 27, 1981	Aug. 27, 1981
Cage/feeder change, animal weight, clinical observations	May 21, 1981	May 28, 1981
12-Month necropsy	Feb. 13, 1981	Feb. 18, 1981
Cage/feeder change, animal weight, clinical observations	Nov. 20, 1980	Nov. 20, 1980
Chronic feeding	June 5, 1980	June 6, 1980
Initiation inspection	Feb. 19, 1980	Feb. 28, 1980
LD_{50}	Jan. 9, 1980	Jan. 9, 1980
Range-finding necropsy	Jan. 9, 1980	Jan. 9, 1980

ACKNOWLEDGMENTS

This program was conducted in the Life Sciences Division under the direction of Dr. David C. L. Jones, Director, Toxicology Laboratory. The experimental work in toxicology was directed by Ted A. Jorgenson, Director, Mammalian Toxicology Department. The chemical and analytical work was directed by Dr. Ronald J. Spanggord, Director, Bio-Analytical Chemistry Program. Dr. Earl F. Meierhenry, Director, Pathology Services Program, and Dr. Daniel P. Sasmore, former Director of Pathology, were responsible for the histopathological evaluation of tissues. Dr. Harold S. Javitz, Director, Data Design and Analyses Department, provided statistical analyses. Ophthalmic examinations were conducted by Dr. Daniel P. Sasmore, Dr. Earl F. Meierhenry, and Dr. Lewis H. Campbell, Veterinary Ophthalmologist. Carol J. Rushbrook, Toxicologist, provided scheduling, coordination, data summary and evaluation, and supervision of the Mammalian Toxicology Department staff; Janice M. Brown, Biologist, subsequently summarized and evaluated the data, supervised the technical staff, and prepared the final report. Sherry J. Hanen, Director, Quality Assurance Unit, reviewed the study. Technical assistance and support were provided by SRI staff chemists (Rodney Keck, Daniel Combs, Michael Regalia, Karyn Raab, David Burris, and Irina Kusnezov), histologists (Barbara Kirkhart and Eileen Paskert), computer programmers (Larry Walters and Lorraine Martin), and biological technicians (Peter Gribling, Sandra Phillips, Juan Dulude, Kathleen Dulude, John Wharton, Robert Harding, Ernestine Seay, Loreli Brown, Steven Halperin, Mark Gilbert, Janet Cortopassi, Kristi Fitzgerald, James Thompson, Mary Mittiga, Richard Romero, Janice Schindler, Jean Yee, Claudia Bouton, and Richard Sartor).

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INTRODUCTION

The overall objective of this research was to provide a comprehensive definition of the long-term toxicological reactions of rodents to LAP (load, assemble, and pack) wastewater, a mixture of the munitions wastewater components TNT and RDX in a ratio of 1.6:1. Specific objectives were to identify, verify, and determine the specificity of possible lesions at the biochemical and cellular levels and to further elucidate dose-response relationships. These data will constitute a significant part of the overall data base necessary to evaluate the potential hazards of these wastewaters to human health and to define the limits of relative safety.

The studies undertaken were (1) confirmatory acute oral LD50 and 14-day range-finding studies of LAP in rats; (2) evaluation of the effect of chronic dietary administration of LAP in rats, and (3) related analytical chemistry studies. These studies were performed in accordance with the FDA Good Laboratory Practice Regulations and the "Guide for Laboratory Animal Facilities and Care," as promulgated by the Committee on the Guide for Laboratory Animal Resources, National Academy of Sciences-National Research Council.

Preliminary animal studies (LD50 and 14-day range-finding) were conducted between 12/13/79 and 1/10/80. The chronic toxicity study was initiated on 2/14/80; all test animals were terminated by 3/5/82. Upon completion of the final report, all records from this project will be permanently transferred to SRI's Records Retention Center.

A copy of the statistical evaluation of the LD50 study, hematology, and clinical chemistry data for the 14-day study, and hematology, clinical chemistry, and organ weight data for the chronic study are on file with the USAMRDC.

MATERIALS AND METHODS

Compound Identification and Purity Analyses

Sufficient quantities of 2,4,6-trinitrotoluene (TNT), Lot #VOL76K014-341, and 1,3,5-trinitrohexahydro-1,3,5-triazine (RDX), Lot #HOL-435-0039, were received from the U.S. Army at SRI's explosives magazine in Tracy, CA, in November 1979. Bulk chemicals were stored at room temperature and were transferred to SRI in limited quantities as needed. Both TNT and RDX were characterized by chemical analysis as follows:

TNT

TNT was identified by its mass spectrum, infrared spectrum, and nuclear magnetic resonance spectrum. All spectra were in agreement with the 2,4,6-trinitrotoluene structure.

The purity of TNT was evaluated through its elemental composition and its homogeneity was established by gas chromatography. The results of elemental analysis are as follows:

	C	H	N
Calculated:	37.00	2.22	18.50
Found:	37.15	2.25	18.18

It should be noted that nitro compounds tend to give low nitrogen results. The carbon and hydrogen results suggest that the TNT is 98.9 to 100.4% pure.

The purity of TNT was evaluated by gas chromatography under the following conditions:

Instrument: Hewlett-Packard 5711A gas chromatograph

Column: 1.8 M x 2 mm Glass column packed with 10% DC-200 on 100/120 mesh Gas Chrom Q

Temperature: 100 to 200°C at 4°/min

Flow rate: 25 ml/min

Detection: Flame ionization

Retention time: 22.4 min.

One major peak eluted at 22.04 min and represented 99.9% of total peak areas. A minor peak representing 0.06% of total peak areas eluted at 18.28 min and was identified by mass spectrometry as 2,4-dinitrotoluene. Another

minor peak eluting at 24.53 min and representing 0.05% of total peak areas was identified as 4-amino-2,6-dinitrotoluene.

Based on the above data, the TNT used in this study is the 2,4,6-isomer with a purity of > 98.7%.

RDX

RDX was identified by its mass spectrum, infrared spectrum, and nuclear magnetic resonance spectrum. All spectra were consistent with the proposed structure for RDX.

The purity of RDX was estimated by elemental analysis and high-pressure liquid chromatography. The results of elemental analysis are as follows:

	C	H	N
Calculated:	16.21	2.72	37.84
Found:	16.36	2.64	37.14

It should be noted that nitro compounds tend to give low nitrogen results. The carbon and hydrogen results suggest that the RDX is 97.1 to 100.9% pure.

The purity of RDX was evaluated by high-pressure liquid chromatography under the following conditions:

Instrument: Spectra-Physics Model 3500B liquid chromatograph

Column: C_{18} Radial Pak A (Waters Associates)

Solvent: Acetonitrile/methanol/water (10/30/60)

Flow rate: 2.0 ml/min

Detection: UV at 254 nm

Retention time: 8.32 min.

A major component eluted at 8.32 min (RDX) and a minor component eluted at 5.78 min. The minor component was identified as HMX by cochromatography with an authentic standard. Based on the response to the UV detector, HMX was present at 5.1% on a weight basis. Three additional evaluations on different samples from the same batch of RDX showed that HMX was present at 9.1, 10.5, and 7.3%. The average HMX concentration was calculated to be 8.0 ± 2.3%.

We conclude from the above data that munition-grade RDX contains HMX as an impurity that is inhomogeneously distributed in the sample matrix and

contributes to 5.1 to 10.5% of the total sample weight. The elemental data do not account for such a large impurity since the elemental ratios for HMX are identical to those of RDX.

Animals

Source

Initially, young-adult, Fischer-344 rats of both sexes (40 to 70 g) were purchased from Simonsen Laboratories, Inc., Gilroy, CA, for both the preliminary and chronic studies. Because the automatic watering system in new racks acquired for the chronic study was not properly flushed by the installer, animals for the chronic study were exposed during quarantine to toxic residues of the glues used in the assembly of the racks. These animals were terminated, the problem was corrected, and a replacement shipment of young-adult Fischer-344 rats of both sexes in the same weight range were purchased for the chronic study from Charles River Breeding Laboratories, Inc., Portage, MI, because Simonsen Laboratories could not provide a replacement shipment in time for initiation of the chronic study.

Housing

All rats were held in an air-conditioned animal room for 5 to 7 days of acclimation for the preliminary studies and for 2 weeks for the chronic study. They were housed five per cage in hanging polycarbonate shoebox cages containing hardwood chip bedding (AbsorbDri) supplied by Gardena Seed and Feeding Corp., Vernon, CA. Animals in each cage were individually identified by ear notches; an identification card on each cage was color-coded to indicate dose level.

Feed

Prior to arrival of the animals, Purina Certified Rodent Chow #5002 and noncertified Purina Rodent Chow #5001 were analyzed for pesticide residues, PCBs, aflatoxins, heavy metals, and nitrate and nitrite anions and a comparison was made.

Feed samples were extracted according to official AOAC methods.[1] The extracts were analyzed for chlorinated organic pesticides by glass-capillary gas chromatography under the following conditions:

Instrument: Varian Model 3740 gas chromatograph

Column: SP-2100 30 M Glass capillary column

Temperature: 220°C

Flow rate: 0.8 ml/min N_2

Detection: Electron capture at 300°C

Injector port temperature: 250°C

Attenuation: 4 Range 10^{-12}.

Analyses for organophosphate pesticides were performed by packed-column gas chromatography under the following conditions:

Instrument: Hewlett-Packard Model 5730A gas chromatograph

Column: 1.8 M x 2 mm Glass column packed with 10% DC-200 on Gas Chrom Q

Temperature: 220°C

Flow rate: 25 ml/min N_2

Detection: Alkali-flame ionization

Injector port temperature: 250°C.

The results of these analyses are as follows:

Chemical	Rodent Laboratory Chow 5001 (ppm)	Certified Rodent Chow 5002 (ppm)	Max. for 5002 Feed as Certified (ppm)
Heptachlor	0.005	0.008	0.05
Aldrin	0.001	not detected	0.05
Heptachlor epoxide	not detected	0.006	0.05
Chlordane	not detected	0.021	0.05
DDE	not detected	0.015	0.15
Dieldrin	0.001	0.001	0.05
Endrin	not detected	0.001	0.05
Phorate	not detected	0.004	0.5
Diazinon	0.001	0.001	0.5
Disulfoton	not detected	0.003	0.5
Methyl parathion	0.002	0.004	0.5
Malathion	0.072	0.110	0.5
Parathion	0.003	0.013	0.5
Ethion	not detected	not detected	0.5

Aflatoxins B_1, B_2, G_1, and G_2 in feed were analyzed by high-pressure liquid chromatography.[2] The results showed that no aflatoxins were present at concentrations greater than 1 ppb.

Feed samples were analyzed for nitrate and nitrite by high-pressure liquid chromatography using an anion exchange column and ultraviolet detection at 210 nm.[3] Neither anion was found at concentrations greater than 100 ppb.

The noncertified diet did not contain contaminant levels greater than those stated or determined for the certified diet; however, the USAMRDC specified the use of Purina Certified Rodent Chow #5002. Diet was supplied ad libitum in all studies. Subsequent information on feed content was provided by the analytical data sheet provided by Purina with each shipment.

Water

Water supplied by the San Francisco Water District was available to the animals through an automatic watering system. Annual San Francisco Water Department analyses of partial chemical, coliform, and inorganic content performed during the course of these studies were within acceptable limits and are on file at SRI. At SRI, the nonfluorinated district water is passed first through an activated charcoal bed and then through cation and anion exchanger columns. Each of these columns can process up to 80,000 gallons of water, and they are changed approximately every 5 weeks. A conductivity light that goes out if the resistance of the water is less than 50,000 ohms is used to determine when the columns need replacement. The deionized water than passes through a 7.5-μ filter and past an ultraviolet lamp. The water in the automatic watering system (except in the "drops" and racks) is recirculated constantly past the lamp and through a mixed bed column and a 5-μ filter to remove any accumulated metals and particulates. A conductivity light that goes out when the water resistance is less than 200,000 ohms is used to determine when this column needs replacement.

Prior to the start of the studies, water from the automatic watering system was analyzed at SRI. On 30 November 1979, one water sample was evaluated for pesticide residues, and another sample was cultured for bacteria. No bacterial colonies grew from the sample. For the pesticide analyses, one liter of water was extracted with diethyl ether, concentrated in a Kurderna-Danish apparatus, and analyzed by glass capillary gas chromatography using electron capture detection. None of the pesticides listed below were observed above the level of 0.1 ppb.

Chlorinated Pesticides	Organophosphate Pesticides
Heptachlor	Phorate
Aldrin	Diazinon
Heptachlor epoxide	Disulfoton
Chlordane	Methyl parathion
DDE	Malathion
Dieldrin	Parathion
Endrin	Ethion

We were unable to get a radioactivity analysis from the supplier, but we believe that the ion exchange treatment would remove any radionuclides as well as stable ions.

During the course of these studies, water from the automatic system was further analyzed annually by Stoner/McIntosh Laboratories, Santa Clara, CA, for heavy metals (detected as H_2S precipitable material), oxidizable organics, and coliforms. Results of these analyses were within acceptable limits and are on file at SRI.

We conclude that the water supplied to the animals was free of known contaminants that would influence the results of these samples.

Dose Preparation and Analyses

For preparation of oral suspensions or diets, the RDX was first filtered from its water slurry and air-dried. For the oral intubation study, the LAP (1.6:1 TNT/RDX) was suspended in acetone and then in corn oil to achieve the necessary concentration; the acetone was removed by rotary evaporation. For the feeding studies, LAP was dissolved in acetone and added to 3% corn oil; the acetone was again removed by rotary evaporation. This compound/residual acetone/corn oil mixture was then incorporated into the finely ground rodent chow and mechanically mixed. Diets were stored at 4°C until use. Chemical stability studies showed that mixed diets were stable for two weeks at room temperature. Accordingly, diets were mixed every two weeks. In the 14-day range-finding studies, LAP was administered as a constant percent in the diet; analyses of LAP concentration in the diet were performed on diet samples from the lowest and highest dose levels. In the chronic studies, diet concentrations were adjusted once every two weeks throughout the study, based on examination of body weight and food consumption trends, to achieve a close approximation of the mg/kg/day target dose levels. Diets prepared during the first 13 weeks and one mixing in each quarter thereafter were analyzed for TNT and RDX by high-pressure liquid chromatography.[4] Samples were saved from each diet mix regardless of whether it was analyzed. The corn oil used in these studies was Gregg's Refined Corn Oil supplied by Fast Food Supply Co., Inc., San Jose, CA, or Domestic Cheese Co., Inc., San Francisco, CA. Each batch of corn oil was assayed for peroxide levels by iodometric titration.[5]

Acute Oral LD50 Study

Ten males and ten females, weighing between 52 and 95 g, were assigned to a vehicle control and six compound treatment levels using a weight-sorting randomization procedure. All animals were fasted overnight before receiving a single oral dose of the test compound by gavage, prepared as previously described. Controls received a corn oil-acetone mixture from which the acetone had been evaporated. The six treatment (LAP) groups received one of the following dose levels: 150, 300, 450, 600, 750, or 900 mg/kg. The animals were closely observed immediately after treatment and several times later that day. Daily observations for physiological and behavioral responses and mortality were continued for 14 days after treatment. Body weights were recorded initially and then weekly during the 2-week observation period. Animals that died during the study were necropsied for evidence of gross pathological changes; all survivors were necropsied at the end of the observation period. No tissues were retained.

LD50 values were calculated by computer-generated statistical programs. The probit method[6] was used for the males, and the binomial method using linear interpolation of log doses provided a point estimate of the LD50 for the females. The results of these studies were used to determine dose levels for the 14-day range-finding study.

14-Day Range-Finding Study

Ten male and ten female rats, weighing between 46 and 94 g, were assigned to each of six experimental groups (vehicle control, 0.05, 0.1, 0.3, 0.5, and 0.7% in the diet). For assignment to treatment groups, rats were weight-sorted into cages, and the cages were assigned to groups using computer-generated sets of random numbers. The compound was administered through the diet, which was prepared as described earlier. The vehicle control group received a feed/corn oil mixture prepared as described above except that the acetone contained no LAP. Body weights and food consumption were recorded weekly. The animals were observed daily for physiological and behavioral responses and mortality for 14 days. Gross necropsies were performed on rats that died during the study and on survivors at the end of the 2-week observation period.

Hematology and clinical chemistry determinations were conducted on all survivors at the termination of the study. The following analyses were performed by Peninsula Medical Laboratory, Menlo Park, CA.

Erythrocyte and Leukocyte Counts (RBC, WBC). A Coulter Electronic Particle Counter with 100 μ aperture was used.[7] The instrument was standardized daily in a three-step process, as follows. The electronics were first checked in a standard procedure for proper functioning. Then the instrument was standardized for erythrocyte and leukocyte counts (as well as hemoglobin and hematocrit) against a 4C control standard (Coulter Electronics, Inc.). Finally, two blood samples that had been kept from the previous day and refrigerated were rerun for erythrocyte and leukocyte counts. Each test blood sample was counted in duplicate.

Hemoglobin (Hgb). Hemoglobin was determined in the Coulter counter as cyanmethemoglobin.[8] Cyanmethemoglobin standards were supplied by Coulter Electronics, Inc., as part of the 4C control standard. Each blood sample was measured in duplicate.

Hematocrit (Hct). Hematocrit was calculated by the equation Hct = RBC ($10^6/mm^3$) x MCV (μ^3).

Mean Corpuscular Volume (MCV). MCV was determined in the Coulter Counter after (daily) standardization by the Wintrobe microhematocrit method. MCV on each test sample was determined in duplicate, and Hct was calculated from the average according to the above equation.

Mean Corpuscular Hemoglobin (MCH). MCH was calculated as follows:

$$\text{MCH } (\mu\mu g) = \frac{\text{Hgb (gm \%) x 10}}{\text{RBC } (10^6/mm^3)}$$

Mean Corpuscular Hemoglobin Concentration (MCHC). MCHC was calculated as follows:

$$\text{MCHC (gm \%)} = \frac{\text{Hgb (gm \%)} \times 100}{\text{Hct}}$$

Differential Leukocyte Counts. Leukocytes were stained with Wright's stain for examination and counting under the microscope. Cell types identified and counted were polymorphonuclear cells, band cells, lymphocytes, monocytes, eosinophils, and/or basophils.

Clinical chemistry tests, representing a SMAC-20 profile as described in the Technicon manual (Technical Publication No. UA3-0306B3, March 1976), were performed using the Technicon SMAC high-speed, computer-controlled biochemical analyzer (Technicon Instruments Corp., Tarrytown, New York). Standardization for each test was made on every forty-eighth tube (sixth rack), using the Technicon SMAC References I and II (FDA-approved) and the procedures outlined in the bulletins accompanying these references (Nos. 4060-A-R8-6/R11-7-2 and 4060 B-R4-7/R11-7-2, Technicon Instruments Corp.).

Glucose (mg %). Blood glucose levels were determined in sera from fasted animals by a modification of the procedures of Gochman and Schmitz.[9] The method basically involves oxidation of glucose with glucose oxidase to produce H_2O_2, which then reacts with 3-methyl-2-benzothiazolinone hydrazone and dimethylaniline indicators to produce an intensely colored indamine dye for determination in the colorimeter at 37°C.

BUN (mg %). The Technicon method used was a modification of the procedure described by Marsh et al.[10] This method entails the hydrolysis of diacetyl monoxime to diacetyl in relatively weak acid solutions and its subsequent reaction with urea in the presence of ferric ions and thiosemicarbazide to intensify the color (analysis at a wavelength of 520 nm).

Creatinine (mg %). Creatinine was analyzed by an automated adaptation[11] of the original method of Jaffe[12] in which the creatinine is allowed to react with saturated picric acid in alkaline solution at 37°C. Analysis in the colorimeter was performed at 505 nm.

Uric Acid (mg %). Uric acid was determined by the method of Sobrinho-Simoes,[13] as modified by Musser and Ortigoza.[14] The method is based on the reduction of a phosphotungstate complex to a phosphotungstite complex with addition of hydroxylamine to intensify the color (observations were made at 660 nm).

Sodium (meq/L). The sodium ion content of sera was determined potentiometrically, using a sodium ion-selective glass electrode.[15]

Potassium (meq/L). Potassium was determined with a potassium ion-selective electrode.[16]

Carbon Dioxide (meq/L). The method for determining carbon dioxide was based on the automated procedure of Skeggs and Hochstrassser.[17] Carbon

dioxide, released first by acid, was determined from the decrease in the red color of an alkaline phenolphthalein solution (at 550 nm).

Chloride (mg/L). Chloride was determined colorimetrically using the automated method of Morgenstern et al.[18] In this method, $Hg(SCN)_2$ reacts with chloride ions in the presence of ferric ions to produce red $Fe(SCN)_3$ (observed at 480 nm).

Calcium (mg %). Calcium was determined complexiметrically using an alkaline solution of 8-hydroxyquinoline.[19] The complex produces a pink color with a maximum absorption at 570 nm.

Phosphorus (mg %). Inorganic phosphorus was determined by the phosphomolybdate method of Daly and Ertinghausen[20] as modified for the automatic analyzer by Amador and Urban.[21] The unreduced phosphomolybdate complex absorbs at 340 nm, and the amount of phosphorus present can be determined by difference.

Balance ($Na-[Cl + CO_2]$). Electrolyte balance is the numerical difference of Na^+ concentration and the sum of the concentrations of Cl^- and of dissolved CO_2.

Cholesterol (mg %). Cholesterol was determined by the automated method of Levine et al.[22] In this method (based originally on that of Huang et al.[23]), cholesterol and sulfuric acid react to form bi-cholestadienyl disulfonic acid, a green compound measured at 630 nm in the colorimeter.

Triglycerides (mg %). Analysis of serum triglycerides involves the enzymatic hydrolysis of the compound to glycerol and free fatty acids.[24] A solution of glycerol kinase and pyruvate kinase in a second channel converts glycerol to pyruvate, which in turn is reduced by NADH and lactic acid dehydrogenase to lactate (followed at 340 nm).

Total Bilirubin (mg %). Determination of total bilirubin in sera, like triglycerides, involves a two-channel system for analysis.[25] The bilirubin was reacted with a caffeine-containing diluent that forms azobilirubin. This solution was then mixed with a strongly alkaline sodium potassium tartate buffer and sulfanilic acid to yield a green complex, which can be quantified at 600 nm against a blank channel containing all reagents except for the diazo compound.

SGOT (mU/ml). Serum glutamic-oxaloacetic transaminase (SGOT) activity was measured by following the rate of change of NADH absorption at 340 nm and 37°C produced by maleate dehydrogenase. The latter enzyme system was coupled with GOT-catalyzed transamination of aspartic acid and α-keto-glutarate in the medium.[26]

SGPT (mU/ml). Serum glutamic-pyruvic transaminase (SGPT) activity was monitored in the same manner as SGOT, except that alanine was substituted for aspartic acid and the coupling enzyme was lactate dehydrogenase.[26]

LDH (mU/ml). Lactate dehydrogenase (LDH) activity was determined directly by monitoring the rate of change in absorption at 340 nm in the presence of added L-lactic acid and NAD^+.[18]

Alkaline Phosphatase (mU/ml). The Technicon method for determination of alkaline phosphatase involves the hydrolysis of stock p-nitrophenyl phosphate solutions by the enzyme in the presence of Mg^{2+} to produce a bright-yellow p-nitrophenol product (monitored at 410 nm and 37°C) at pH 10.25.[2]

Total Iron (mcg %). Serum iron was determined by reacting 3-(2-pyridyl)-5,6-bis-(4-phenylsulfonic acid)-1,2,4-triazine (trademarked as FerroZine) in the presence of ascorbic acid to liberate transferrin-bound iron.[28] The FerroZine complex in a sodium acetate medium was measured colorimetrically at 560 nm.

Total Protein (g %). The method for determination of total protein was based on the biuret method, automated for use with the Technicon analyzer.[16]

Albumin (g %). The Technicon method utilizes the reactivity of albumin with bromcresol green (BCG) to form an albumin-BCG complex that can be quantified colorimetrically at 630 nm.[29]

Globulin (g %). Globulin is the difference between total protein and albumin determinations.

A/G Ratio. The albumin-to-globulin (A/G) ratio was calculated individually for each animal sample, and the ratios were averaged for each group by a computer program.

The following tissues were taken from all rats and preserved for possible histological examination:

- Brain (3 sections)
- Heart
- Liver
- Kidneys
- Spleen
- Gonads
- Adrenals
- Pituitary
- Eyes (if grossly abnormal)
- Trachea
- Thyroids/parathyroids
- Mesenteric lymph nodes
- Thymus (if present)
- Lung and mainstream bronchi
- Diaphragm
- Esophagus
- Stomach (cardiac and pyloric)
- Small intestine (duodenum, ileum, jejunum)
- Caecum
- Mammary gland
- Spinal cord (if neurological signs were present)
- Skin
- Colon (sigmoid)
- Pancreas
- Cervical lymph node
- Urinary bladder
- Uterus
- Prostate
- Sternum
- Abnormal tissue
- Mandibular lymph node
- Salivary gland

Histopathological examinations were conducted on the testes of rats in both the control and 0.5% treatment level.

Body weight and hematology data were statistically analyzed by (1) Williams' test, [30,31] (2) Finney's ratio test,[6] (3) a linear trend test,[32] and (4) Bartlett's chi-square test[33]. Food consumption data were statistically analyzed by analysis of variance (ANOVA) and the t-test.[34]

The results of these studies were used to determine dose levels for the chronic study.

Chronic Study

Three dose levels were selected for the chronic study: 12.5, 50.0, and 200 mg/kg/day. Each treatment group consisted of 70 male and 70 female rats. A vehicle control group contained 75 rats of each sex. For assignment to treatment groups, rats were weight-sorted into cages that were assigned to groups using computer-generated sets of random numbers. When placed on test, the male rats weighed between 95 and 142 g, and the females weighed 73 to 110 g. All animals were either 6 or 7 weeks of age. Individual body weights and food consumption by cage were recorded weekly. At this time, cages and racks were rotated within the animal room. Room temperature was recorded daily. The eyes of each animal were dilated and examined initially, at 1 year, and again at the end of the 2-year exposure period. Only rats with normal eyes at the initial examination were randomized into test groups.

The rats were observed daily for physiological and behavioral responses and mortality throughout the 24-month duration of the study. Starting in the ninth month of the study, the rats were palpated during routine weekly handling for evidence of internal masses. Moribund animals and any animals discovered dead were necropsied and submitted for histopathological examination as described later in this report.

Because of signs of excessive toxicity in the male rats receiving 200 mg/kg/day, the high-dose level was lowered to 100 mg/kg/day after 12 weeks on test. Mortality continued to occur, and after 33 weeks on test, all remaining male and female rats at this level were necropsied. Organ weights were taken and histopathology was performed on these animals; hematology and clinical chemistry evaluations were not conducted.

After 12 months on test, 10 males and 10 females from each treatment group (including the vehicle control) were necropsied and examined for pathological changes. Animals for this interim evaluation were taken from the highest numbered cages per group, after a statistical assessment (analysis of variance) of body weights showed no rack- or cage-related effects. After 24 months on test, all remaining animals were necropsied over a 2-week period. Hematology and clinical chemistry evaluations, as described for the 14-day range-finding study, were performed on all rats at the interim necropsy (12 months) and on 20 rats per sex at the terminal necropsy. A reticulocyte count was also included.

At necropsy, performed on all rats, the tissues identified in the 14-day range-finding study were preserved. A section of the thoracic/lumbar spinal cord and vertebrae and the rectum were also taken from animals at the terminal necropsy. Absolute organ weights of the brain, heart, liver, kidneys, spleen, and testes were recorded. Histopathological examination was performed on all preserved tissues.

The body and organ weight, hematology, and food consumption data were analyzed as described for the 14-day range-finding study.

Lesions observed in the low- and mid-dose animals surviving more than one year on study, and tumors with an incidence of 5% or greater in any group, regardless of time of death, were statistically analyzed by Fisher's exact probability test.

RESULTS AND DISCUSSION

Acute Oral LD50 Study

Table 1 summarizes the acute oral toxicity of LAP in rats. The majority of deaths were preceded by decreased activity, salivation, and lacrimation; convulsions and dyspnea were also frequently noted. Other clinical signs or conditions noted in some animals prior to death included prostration, humped back, cyanosis, hyperactivity, ataxia, nasal exudate, chromodacryorrhea, and opisthotonos. All rats receiving LAP had red urine approximately 1 hour after treatment. In addition to the red urine, the survivors also had transient signs of decreased activity, salivation, rough fur, and a humped appearance. Average body weights are presented in Table 2; all survivors from the treated groups gained weight throughout the 2-week observation perod. Necropsy of the animals that died revealed no gross abnormalities. Emphysema, atelectasis, petechial hemorrhage, and/or congestion of the lungs were noted in a few of the rats surviving treatment.

One male in the vehicle control group died 12 days after treatment. Beginning 7 days after treatment, this animal had a humped appearance and was emaciated; a bloody nasal exudate was also noted. Necropsy revealed marked emphysema and moderate atelectasis and congestion of the lungs. All other control rats appeared normal and gained weight throughout the 2-week observation period. An incidence of respiratory disease similar to that in the treated animals was noted at necropsy of the surviving control rats.

The acute oral LD50 of LAP in male Fischer-344 rats was calculated by the probit method to be 294 mg/kg, with a 95% confidence interval of 200 to 367 mg/kg (Figure 1). Since none of the doses given to the female groups resulted in a mortality rate of 35% or less, the binomial method of linear interpolation was the most appropriate method of statistical analysis. Based on this method, a point estimate of the acute oral LD50 for female rats was calculated to be 325 mg/kg, with confidence limits of negative infinity to 450 mg/kg.

14-Day Range-Finding Study

Red urine was observed in all rats receiving LAP in the diet. Rats receiving the two higher dietary levels (0.5 and 0.7%) showed clinical signs of toxicity including rough fur, a humped appearance, and a decrease in activity. Three males receiving 0.5% of LAP in the diet died during the 14-day study. Of the ten male and ten female rats receiving 0.7%, only one male survived for the duration of the study; one male and two females were necropsied early when found moribund, and the remainder were found dead. Rats receiving either the vehicle control or one of the three lower dose levels of LAP (0.05, 0.1, and 0.3%) exhibited no clinical abnormalities during the study.

Table 1

ACUTE ORAL TOXICITY OF LAP ADMINISTERED
TO MALE AND FEMALE FISCHER-344 RATS

LD50 Study

Sex	Dose Level (mg/kg)	No. Dead/ No. Treated	Time to Death	LD50 (mg/kg)
Male	0	1/10	12 days	
	150	2/10	1-4 hrs	
	300	5/10	5-29 hrs	294
	450	8/10	2-21 hrs	(200-367)
	600	10/10	1-21 hrs	
	750	10/10	2-50 hrs	
	900	10/10	1-4 hrs	
Female	0	0/10	—	
	150	4/10	2-6 hrs	
	300	4/10	3-21 hrs	325
	450	9/10	1-28 hrs	(neg. infinity-450)
	600	10/10	3-27 hrs	
	750	10/10	3-21 hrs	
	900	10/10	1-4 hrs	

*95% Confidence limits in parentheses.

Table 2

AVERAGE BODY WEIGHTS (g) OF RATS TREATED ORALLY WITH LAP

LD50 Study

Sex	Dose (mg/kg)	Day 0	Day 7	Day 14	Gain
Male	0	74.1	107.0	142.2 (9)*	68.1
	150	71.4	103.4 (8)	137.3 (8)	65.9
	300	74.1	100.0 (5)	137.6 (5)	63.5
	450	73.7	106.5 (2)	139.5 (2)	65.8
	600	71.1	—	--	—
	750	74.3	--	--	--
	900	75.8	—	--	--
Female	0	69.6	94.4	114.2	44.6
	150	66.6	92.0 (6)	113.8 (6)	47.2
	300	66.5	93.8 (6)	113.2 (6)	46.7
	450	68.4	90.0 (1)	111.0 (1)	42.6
	600	68.7	--	—	--
	750	69.1	—	--	--
	900	69.5	--	--	--

*Number of survivors in parentheses.

****** PROBIT METHOD ******

LINEAR DOSE MODEL

LOWER 95 PCT LIMIT	LD50 ESTIMATE	UPPER 95 PCT LIMIT
200.1	294.0	367.3

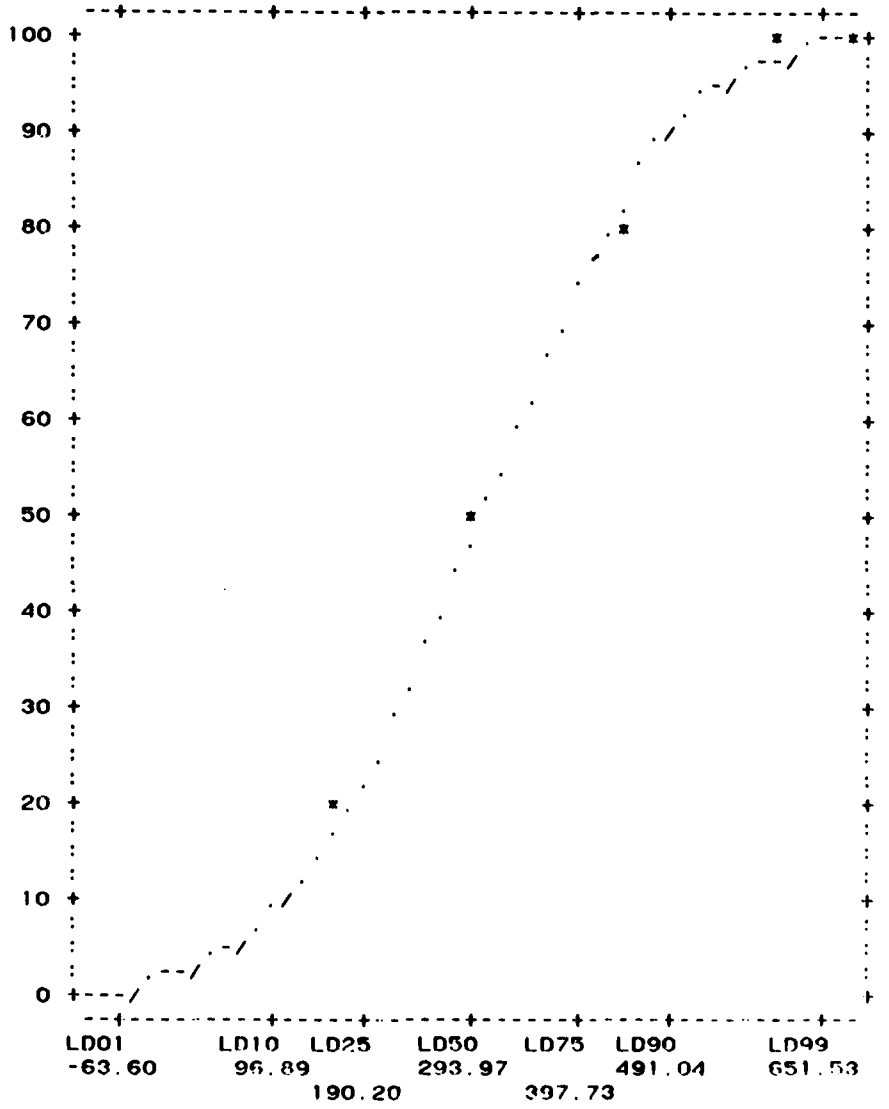


FIGURE 1 PROBIT CURVE FOR MALE RATS TREATED ORALLY WITH LAP--LD50 STUDY

Table 3 summarizes the body weight data during the 2 weeks of treatment. These data are illustrated in Figures 2 and 3 for males and females, respectively. After 1 week on test, the males weighed significantly less than the controls, beginning at the 0.1% level; females weighed significantly less compared with controls, beginning at the 0.3% level. Weekly body weight gains after 1 and 2 weeks are presented in Table 4 in which significant recoveries toward control values from Week 1 to Week 2 in both sexes are shown.

Closely correlated with the body weight losses were decreases in food consumption in rats of both sexes. Table 5 presents the food consumption data based on grams of food consumed per day; Table 6 presents food consumption data based on grams of food consumed per day per kilogram of body weight. The results show a definite dose-related response during Week 1, with indications of recovery toward control values during Week 2.

Results of the hematology and clinical chemistry analyses are presented in Tables 7 and 8, respectively. In the males, hematology parameters reflected high toxicity at the 0.5% level. Some parameters were significantly affected at all dose levels. At comparable levels, most parameters appeared slightly less affected in the females. Again, some parameters were affected at all dose levels. Numerous clinical chemistry values were significantly affected beginning at the 0.3% level for both sexes. In the males, only triglycerides, LDH, and alkaline phosphatase were signficantly affected (decreased) at the lowest dose level (0.05%). In the females, the lowest dose animals were not affected, and only the triglycerides were significantly decreased at the 0.1% level.

Summaries of findings from the terminal necropsies of the males and females are presented in Tables 9 and 10, respectively. The testes of all seven male survivors receiving 0.05% of LAP in the diet and of the one surviving male at the 0.7% level were smaller compared with controls. The prostate and seminal vesicles of many of these rats also appeared smaller. For a more specific evaluation of this finding, the testes from control rats and from rats at the 0.5% level were examined histologically. Evidence of immaturity and delayed development was seen histologically, correlating with the 46% reduction in body weights of male rats after 2 weeks of treatment at this dose level, relative to control males (Figure 2). Degenerative or inflammatory changes were not detected.

Chronic Study

Dose Level Determinations

Based on the data collected from the 14-day range-finding study, dietary levels equivalent to 12.5, 50, and 200 mg/kg/day were selected for the chronic study. These dose levels meet the basic criteria of the EPA dose selection guidelines for both oncogenic and nononcogenic chronic effects test standards. They allow for a dose-response analysis, with the high-dose level (HDL) resulting in toxicity, the intermediate dose being one-half to one-quarter of the high dose, and the low dose being a "no observed effect level" (no more than one-half of the intermediate dose).[35]

Table 3

BODY WEIGHTS (g) OF MALE AND FEMALE RATS TREATED WITH LAP

14 Day Range-Finding Study

Sex	DEPENDENT VARIABLE	CONTROL GROUP	TREATMENT GROUPS 0.05 % T R	0.1% T R	0.3% T R	0.5 % T R	0.7 % T R
Male							
	INITIAL	75.60 (3.22)	79.20 (2.34)	77.90 (3.67)	79.10 (3.53)	77.00 (3.49)	77.90 (3.27)
	WEEK 1	105.70 (3.29)	101.30 (2.08)	93.60 (4.09) *	76.30 (3.83) + A	59.44 (2.65) + C	52.33 (7.84) + C
	WEEK 2	142.60 (3.63)	135.20 (5.59)	124.90 (4.41) +	92.80 (3.96) + B	65.14 (3.47) + C	70.00 (0.00) + B
Female							
	INITIAL	68.00 (3.14)	70.80 (3.01)	70.80 (2.75)	68.50 (3.76)	69.00 (2.82)	68.40 (3.50)
	WEEK 1	85.30 (3.57)	86.50 (3.56)	78.80 (3.86)	63.80 (3.60) + A	54.90 (1.23) + B	57.00 (0.00) + B
	WEEK 2	106.50 (3.71)	108.70 (4.10)	97.90 (5.00)	74.40 (3.70) + B	61.30 (1.35) + C	

ENTRIES ARE MEANS WITH STANDARD ERRORS IN PARENTHESES
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
CONFIDENCE INTERVAL IS HIGHER OR LOWER THAN MEAN BY AT LEAST : 10 PERCENT - A, 20 PERCENT - B,
35 PERCENT - C OR 50 PERCENT - D

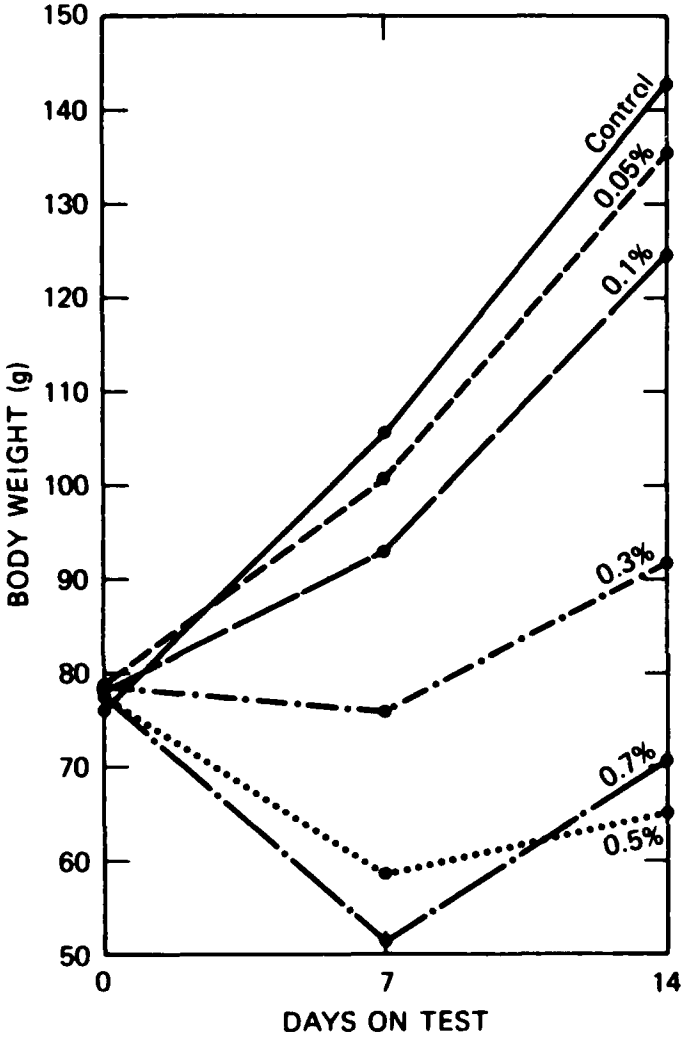


FIGURE 2 AVERAGE BODY WEIGHTS OF MALE RATS TREATED WITH LAP

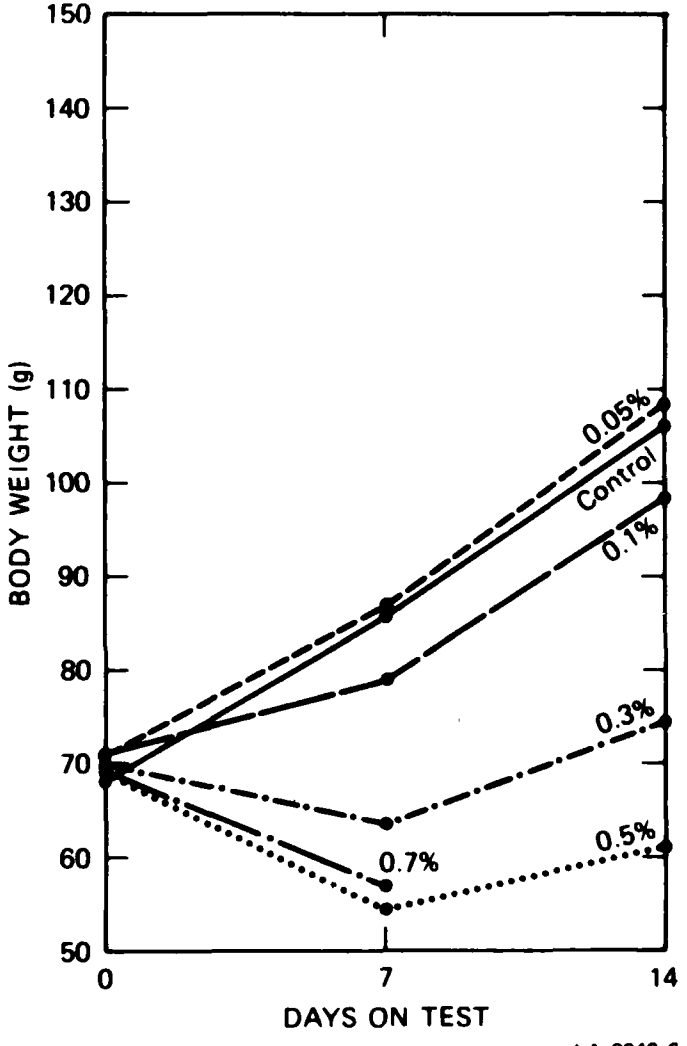


FIGURE 3 AVERAGE BODY WEIGHTS OF FEMALE RATS TREATED WITH LAP

14 DAY RANGE-FINDING STUDY

Table 4

WEEKLY BODY WEIGHT GAIN (g) OF MALE AND FEMALE RATS TREATED WITH LAP

14 Day Range-Finding Study

Sex	DEPENDENT VARIABLE	CONTROL GROUP	TREATMENT GROUPS 0.05 % T R	0.1 % T R	0.3% T R	0.5% T R	0.7 % T R
Male							
	WEEK 1	30.10 (1.05)	22.10 (2.82) *	15.70 (1.44) + C	-2.80 (1.53) + D	-16.89 (1.97) + D	-25.67 (6.17) * D
	WEEK 2	36.90 (1.02)	33.90 (3.99)	31.30 (.883) +	16.50 (1.19) + C	5.43 (3.04) + D	5.00 (0.00) + D
Female							
	WEEK 1	17.30 (1.65)	15.70 (1.24)	8.00 (2.29) + B	-4.70 (1.28) + D	-14.10 (1.92) + D	-24.00 (7.00) + D
	WEEK 2	21.20 (.998)	22.20 (.964)	19.10 (2.12)	10.60 (.991) + C	6.40 (.872) + D	

ENTRIES ARE MEANS WITH STANDARD ERRORS IN PARENTHESES
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
T = TREATMENT-CONTROL CONTRAST ; R = TREATMENT-CONTROL RATIO TEST
CONFIDENCE INTERVAL IS HIGHER OR LOWER THAN MEAN BY AT LEAST : 10 PERCENT - A, 20 PERCENT - B,
35 PERCENT - C OR 50 PERCENT - D

Table 5

FOOD CONSUMPTION (g/day) OF MALE AND FEMALE RATS TREATED WITH LAP

14 Day Range-Finding Study

Sex	DEPENDENT VARIABLE	CONTROL GROUP	TREATMENT GROUPS 0.05 %	W	0.1 %	W	0.3 %	W	0.5%	W	0.7 %	W
Male												
	WEEK 1	12.0 (.271)	10.4 (.357)	*	9.0 (.014)	*	5.1 (.014)	*	2.8 (.414)	*	1.2 (.099)	*
	WEEK 2	13.4 (.186)	12.2 (.714)		11.4 (.186)		8.1 (.371)	*	5.0 (.166)	*	5.4 (0.00)	*
Female												
	WEEK 1	8.6 (.429)	8.4 (.186)		6.9 (.114)		3.9 (.400)	*	2.5 (.500)	*	.6 (.548)	*
	WEEK 2	9.5 (.243)	9.2 (.071)		8.5 (.086)	*	6.3 (.114)	*	4.9 (.129)	*		

ENTRIES ARE CAGE MEANS WITH STANDARD ERRORS IN PARENTHESES
W = WILLIAMS TEST OF LOWEST SIGNIFICANT CONTROL-TREATMENT COMPARISON
* CONFIDENCE LEVEL = .95

Table 6

FOOD CONSUMPTION (g/kg body weight/day) OF MALE AND FEMALE RATS TREATED WITH LAP

14 Day Range-Finding Study

Sex	DEPENDENT VARIABLE	CONTROL GROUP	TREATMENT GROUPS 0.05 %	W	0.1%	W	0.3%	W	0.5 %	W	0.7 %	W
Male												
	WEEK 1	113.2 (.965)	102.8 (1.19)		95.7 (1.46)	*	66.9 (1.30)	*	46.9 (4.90)	*	22.2 (2.40)	*
	WEEK 2	94.1 (.941)	90.2 (.747)		90.9 (.249)		86.8 (.302)		76.7 (4.06)	*	76.8 (0.00)	*
Female												
	WEEK 1	100.8 (1.60)	96.9 (1.81)		87.8 (2.34)		61.4 (6.46)	*	44.9 (8.21)	*	10.8 (9.61)	*
	WEEK 2	89.5 (.492)	85.0 (.110)		86.8 (2.40)		84.5 (.173)		79.5 (1.97)	*		

ENTRIES ARE CAGE MEANS WITH STANDARD ERRORS IN PARENTHESES
W = WILLIAMS TEST OF LOWEST SIGNIFICANT CONTROL-TREATMENT COMPARISON
* CONFIDENCE LEVEL = .95

Table 7

HEMATOLOGY ANALYSES OF RATS TREATED WITH LAP

14-Day Range-Finding Study

Treatment Group	WBC x10³	RBC x10⁶	Hgb gm %	Hct %	MCV μ³	MCH μμg	MCHC %	Differential Count (%) PMN	Band	Lymph	Mono	Eosino	Baso
Males													
Control	7.2 ± 1.5 (7)*	7.22 ± 0.4 (9)	13.6 ± 0.8 (9)	41.3 ± 1.7 (9)	56 ± 1.0 (9)	18.7 ± 0.3 (9)	32.9 ± 0.9 (9)	16 ± 5.6	0	83 ± 5.9	1.5 ± 1.5	0.1 ± 0.3	0
0.05%	6.3 ± 1.8	7.27 ± 0.6	13.3 ± 1.0	40.2 ± 3.0	54 ± 0.7**	18.1 ± 0.3**	33.1 ± 0.5	23 ± 10.4	0	75 ± 9.9	2.3 ± 2.0	0.3 ± 0.5	0
0.1%	6.5 ± 2.1	7.31 ± 0.2	13.1 ± 0.5	39.8 ± 1.3	53 ± 1.1**	17.7 ± 0.4**	32.9 ± 0.6	24 ± 11.1**	0	76 ± 11.0	0.4 ± 0.5	0.1 ± 0.3	0
0.3%	7.4 ± 2.2	7.11 ± 0.3	12.4 ± 0.6**	38.0 ± 1.7**	52 ± 1.0**	17.3 ± 0.4**	32.8 ± 0.6	30 ± 7.8**	0.2 ± 0.4	68 ± 8.0**	1.9 ± 1.1	0.3 ± 0.5	0
0.5%	3.5 ± 1.0** (5)	6.21 ± 0.5** (7)	11.6 ± 0.7** (7)	34.0 ± 2.6** (7)	53 ± 2.0** (7)	18.4 ± 0.7 (7)	34.2 ± 1.1** (7)	39 ± 14.8** (7)	0.6 ± 0.8** (7)	58 ± 15.4** (7)	2.4 ± 1.6 (7)	0.3 ± 0.5 (7)	0 (7)
0.7%	6.8 (1)	5.58** (1)	11.2** (1)	32.0** (1)	55 (1)	19.7† (1)	34.8† (1)	41† (1)	0 (1)	58† (1)	1 (1)	0 (1)	0 (1)
Females♦													
Control	5.5 ± 3.3	7.33 ± 0.6	13.7 ± 0.9	40.5 ± 2.6	55 ± 1.5	18.5 ± 0.6	33.6 ± 0.8	20 ± 5.5	0.1 ± 0.3	77 ± 6.3	2.5 ± 1.6	0.8 ± 0.8	0
0.05%	5.0 ± 1.0	7.39 ± 0.3	13.6 ± 0.6	41.4 ± 1.7	55 ± 1.1	18.2 ± 0.4	32.6 ± 0.8†	20 ± 7.9	0	78 ± 8.7	2.4 ± 1.3	0**	0
0.1%	5.4 ± 1.5 (9)	7.30 ± 0.5 (9)	13.2 ± 0.8 (9)	40.4 ± 2.6 (9)	54 ± 0.9 (9)	17.9 ± 0.5 (9)	32.6 ± 0.7† (9)	26 ± 10.2	0.1 ± 0.3	73 ± 10.0	1.1 ± 1.4	0.6 ± 0.7	0
0.3%	4.8 ± 1.6	7.47 ± 0.3	12.8 ± 0.6	39.6 ± 1.2	53 ± 1.2	17.2 ± 0.5	32.1 ± 1.0**	40 ± 14.8**	0	58 ± 13.9**	2.0 ± 1.8	0.7 ± 0.5	0
0.5%	10.4 ± 6.0** (8)	6.05 ± 2.0** (8)	13.0 ± 7.6 (8)	39.0 ± 21.5 (8)	61 ± 10.9** (8)	20.5 ± 4.0† (8)	33.1 ± 1.0 (8)	33 ± 10.2**	0.2 ± 0.6	61 ± 7.9**	1.8 ± 2.2	0.8 ± 0.8	0

* Number of rats in sample if different from 10.
** $p < 0.01$.
† $p < 0.05$.
♦ All females at the 0.7% level died.

Table 8

CLINICAL CHEMISTRY ANALYSES OF RATS TREATED WITH LAP

14-Day Range-Finding Study

Parameter Examined	Treatment Group - Males				Treatment Group - Females*						
	Control	0.05%	0.1%	0.3%	0.5% (7)**	0.7% (1)	Control	0.05%	0.1%	0.3%	0.5% (7)
Glucose (mg %)	153 ± 45	157 ± 66	142 ± 43	106 ± 58†	29 ± 13#	34†	107 ± 47	110 ± 50	91 ± 54	48 ± 41#	20 ± 12#
BUN (mg %)	14 ± 6.2	14 ± 6.1	13 ± 4.8	11 ± 5.5	4 ± 1.1#	5	12 ± 6.9	11 ± 5.8	9 ± 5.0	7 ± 5.5	5 ± 0.9†
Creatinine (mg %)	0.5 ± 0.14	0.5 ± 0.16	0.4 ± 0.11	0.4 ± 0.20	0.2 ± 0#	0.2	0.4 ± 0.14	0.4 ± 0.14	0.3 ± 0.15	0.2 ± 0.15	0.2 ± 0.04†
Uric acid (mg %)	2.3 ± 1.0	2.4 ± 1.0	2.4 ± 0.9	2.1 ± 1.1	0.6 ± 0.2#	0.7	2.1 ± 1.0	2.2 ± 1.0	2.0 ± 1.1	0.9 ± 0.8#	1.0 ± 0.4†
Na^+ (meq/L)	146 ± 1.2	146 ± 2.5	147 ± 1.2	147 ± 2.4†	151 ± 1.1#	150†	148 ± 1.6	148 ± 2.3	149 ± 1.6	150 ± 2.3#	152 ± 0.8#
K^+ (meq/L)	5.3 ± 1.9	5.5 ± 2.2	5.5 ± 1.6	3.7 ± 1.8†	1.6 ± 0.3#	1.5†	3.9 ± 1.8	4.2 ± 1.6	3.7 ± 1.7	2.6 ± 1.5	2.2 ± 0.6†
CO_2 (meq/L)	16 ± 7.7	17 ± 8.1	17 ± 7.1	10 ± 6.5	2 ± 1.3#	4	11 ± 6.2	12 ± 7.3	10 ± 6.2	5 ± 5.4†	2 ± 1.8#
Cl^- (meq/L)	109 ± 17.3	109 ± 19.6	111 ± 14.5	124 ± 14.2†	145 ± 3.6#	145†	122 ± 17.5	119 ± 17.7	124 ± 14.5	135 ± 11.9†	142 ± 2.8#
Calcium (mg %)	9.0 ± 3.3	9.0 ± 3.7	8.8 ± 2.7	6.2 ± 2.9†	2.4 ± 0.4#	2.6†	6.8 ± 3.2	7.4 ± 3.4	6.2 ± 3.2	3.8 ± 2.6†	2.7 ± 0.4#
Phosphorus (mg %)	8.7 ± 3.0	7.6 ± 3.5	8.2 ± 2.0	5.6 ± 2.4#	2.6 ± 0.6#	2.1†	6.0 ± 2.8	7.1 ± 2.9	5.5 ± 2.7	4.4 ± 2.2	3.5 ± 1.2†
Balance ($Na-[Cl + CO_2]$)	20 ± 9.6	19 ± 10.0	18 ± 7.0	13 ± 5.7†	3.3 ± 2.4#	1†	14 ± 11.0	18 ± 11.4	15 ± 7.5	11 ± 4.9	8 ± 1.7
Cholesterol (mg %)	57 ± 18.1	62 ± 23.8	65 ± 17.9	53 ± 20.6	27 ± 4.6#	38	52 ± 20.5	59 ± 25.0	54 ± 21.0	41 ± 21.2	33 ± 7.3
Triglycerides (mg %)	91 ± 46	49 ± 23#	65 ± 43	43 ± 24#	25 ± 13#	21†	24 ± 17	16 ± 12	12 ± 9†	9 ± 5#	17 ± 14
Total bilirubin (mg %)	0.08 ± 0.04	0.08 ± 0.04	0.10 ± 0	0.08 ± 0.04	0.09 ± 0.04	0.10	0.05 ± 0.05	0.09 ± 0.03	0.07 ± 0.05	0.05 ± 0.05	0.10 ± 0†
SGOT (mU/ml)	267 ± 114	187 ± 98	242 ± 144	116 ± 47#	88 ± 73#	51†	318 ± 218	238 ± 110	222 ± 144	184 ± 131	240 ± 182
SGPT (mU/ml)	110 ± 46	74 ± 41	93 ± 58	37 ± 18#	19 ± 10#	10†	105 ± 77	89 ± 43	82 ± 63	47 ± 42†	53 ± 41
LDH (mU/ml)	1529 ± 602	925 ± 360#	1167 ± 385	672 ± 369#	325 ± 187#	267#	1729 ± 1276	1486 ± 741	1183 ± 499	827 ± 480#	846 ± 231†
Alkaline phosphatase (mU/ml)	824 ± 345	622 ± 271†	550 ± 140#	335 ± 155#	118 ± 36#	117#	393 ± 175	431 ± 175	346 ± 181	192 ± 88#	128 ± 30#
Total iron (mcg %)	217 ± 99	293 ± 221	196 ± 58	191 ± 156	77 ± 7†	88	202 ± 103	182 ± 80	162 ± 113	116 ± 126	70 ± 22#
Total protein (gm %)	4.8 ± 1.6	4.9 ± 1.8	4.8 ± 1.4	3.7 ± 1.5	1.5 ± 0.3#	1.7†	3.8 ± 1.5	4.4 ± 1.7	3.6 ± 1.6	2.3 ± 1.3†	1.8 ± 0.2#
Albumin (gm %)	2.4 ± 0.8	2.4 ± 1.0	2.4 ± 0.8	1.8 ± 0.8	0.7 ± 0.1#	0.8	1.9 ± 0.9	2.2 ± 0.9	1.8 ± 1.0	1.1 ± 0.7†	0.8 ± 0.1#
Globulin (gm %)	2.4 ± 0.8	2.5 ± 0.9	2.4 ± 0.6	1.9 ± 0.7	0.8 ± 0.2#	0.9†	1.9 ± 0.7	2.2 ± 0.8	1.8 ± 0.7	1.2 ± 0.6†	0.9 ± 0.1#
A/G ratio	1.00 ± 0.11	0.97 ± 0.19	1.00 ± 0.11	0.90 ± 0.18	1.01 ± 0.18	0.97	0.97 ± 0.23	0.98 ± 0.11	0.93 ± 0.24	0.95 ± 0.15	0.90 ± 0.10

* All females at the 0.7% level died.
** Number of rats in sample if different from 10.
† $p < 0.05$.
\# $p < 0.01$.

Table 9

GROSS NECROPSY FINDINGS IN MALE RATS TREATED WITH LAP

14-Day Range-Finding Study

Organ	Gross Findings	Treatment Group					
		Control (10)*	0.05% (10)	0.1% (10)	0.3% (10)	0.5% (8)	0.7% (7)
Brain	Hemorrhagic					1†	
Cervical nodes	Hemorrhagic	1	3		1		
Thymus	Small					1	
	Hemorrhagic						1†
Lungs	Hemorrhagic						1†
	Hemorrhagic, emphysema					1†	
	Atelectasis			1			
	Abscess				1		
	Atelectasis, abscess, emphysema	1	1				
Liver	Mottled, pitted			1			
	Light area				1		
Spleen	Dark					1	
	Dark, large					2	1
Stomach	Hemorrhagic					1†	4†
Kidneys	Mottled					1†	
Adrenals	Hemorrhagic				1		
	Dark, large						1†
Seminal vesicles	Small				1	6	1
Prostate	Small					4	
Testes	Small					6	1
	Small, soft					1	

*The number of rats with tissues examined. Tissues from two and three rats in the 0.5 and 0.7% groups, respectively, were lost to autolysis or cannibalization.
†Found dead or moribund during the 14-day treatment.

Table 10

GROSS NECROPSY FINDINGS IN FEMALE RATS TREATED WITH LAP

14-Day Range-Finding Study

Organ	Gross Findings	Treatment Group					
		Control (10)*	0.05% (10)	0.1% (10)	0.3% (10)	0.5% (10)	0.7% (2)
Pituitary	Light in color					2	
Cervical nodes	Hemorrhagic		1	1			
Thymus	Small					3	
Lungs	Atelectasis	1			1		
	Emphysema	1					
	Emphysema, hemorrhagic						1†
	Atelectasis, abscess	1					
	Atelectasis, abscess, emphysema			1	1		
Stomach	Hemorrhagic						1†
Cecum	Hemorrhagic				2		
Adrenals	Hemorrhagic			1		2	1†
Ovaries	Cystic	1					

* Number of rats with tissues examined. Tissues from eight rats in the 0.7% group were at least partially lost to autolysis or cannibalization.

† Found dead or moribund during the 14-day treatment.

Table 11 presents the average doses of LAP, TNT, and RDX received in the chronic study.

Weekly data on dose utilization and cumulative average doses of LAP received weekly for male and female rats are presented in Appendices A and B. Because of excessive toxicity in the males receiving 200 mg/kg/day, the high-dose level was reduced from 200 to 100 mg/kg/day for both sexes, beginning at Week 13. Excessive toxicity and mortality continued to occur, and all surviving high-dose rats were terminated after 33 weeks on test. Assuming that 100% of the intended compound was available in the diet, the average doses received over the 33-week study were 135.90 and 135.71 mg/kg/day for the high-dose males and females, respectively. The weekly doses received ranged from 86.77 to 232.58 mg/kg/day for the males, and 97.27 to 233.33 mg/kg/day for the females.

After 104 weeks on test, the average weekly doses received were within 2% of the target doses of 12.5 and 50 mg/kg/day for the low- and mid-dose levels. The values for these groups were 12.40 and 50.11 mg/kg/day for males and 12.32 and 49.83 for females, respectively. Weekly doses for these groups ranged from 79.5 to 110.2% and 78.7 to 115.1% of the intended dose for males and 69.9 to 109.8% and 70.4 to 110.2% for females. In all cases, the lowest values in the ranges occurred during the second week of the study before dose levels were adjusted with regard to body weight and food consumption trends. The intended LAP concentrations (in ppm) are presented in Appendix C, along with the required analyses of the diet preparations. The last analyses were performed on the diets prepared for Weeks 95 and 96; five additional diets were prepared during the final quarter of the study.

Food Consumption

The average weekly food consumption values (g/day) for male and female rats are presented in Appendices D and E, respectively. These data are graphically presented in Figures 4 and 5 for male and female rats, respectively, based on percent change in food consumption relative to controls. Males in the mid- and high-dose groups showed a consistent, generally significantly, low food consumption compared with the controls, beginning in the first week on test. With the lower LAP content in the diet, beginning with Week 13, food consumption in the high-dose males began to increase, but it remained significantly lower than controls through Week 16. Beginning at Week 17, food consumption of the high-dose males exceeded that of the controls. This trend continued through Week 33 (significantly so during Weeks 28 through 31), when all high-dose males were terminated. Food consumption for the mid-dose males also began to increase and occasionally exceeded control values beginning at Week 24. A statistically significant increase in food consumption was seen in the mid-dose males during Weeks 39 through 45; this trend continued throughout the study and was significant at times. Food consumption in the low-dose males was generally lower than in controls throughout the study; this trend was significant only during Week 15.

Beginning with the first week on test, high-dose females consumed significantly less than controls through Week 10. From Week 13, when the dose level was reduced, food consumption in the high-dose females began to exceed that of the controls; from Week 23 and continuing until the group was terminated (Week 34), this increase was often significant. Food consumption was significantly low in the mid-dose females from Weeks 4

Table 11

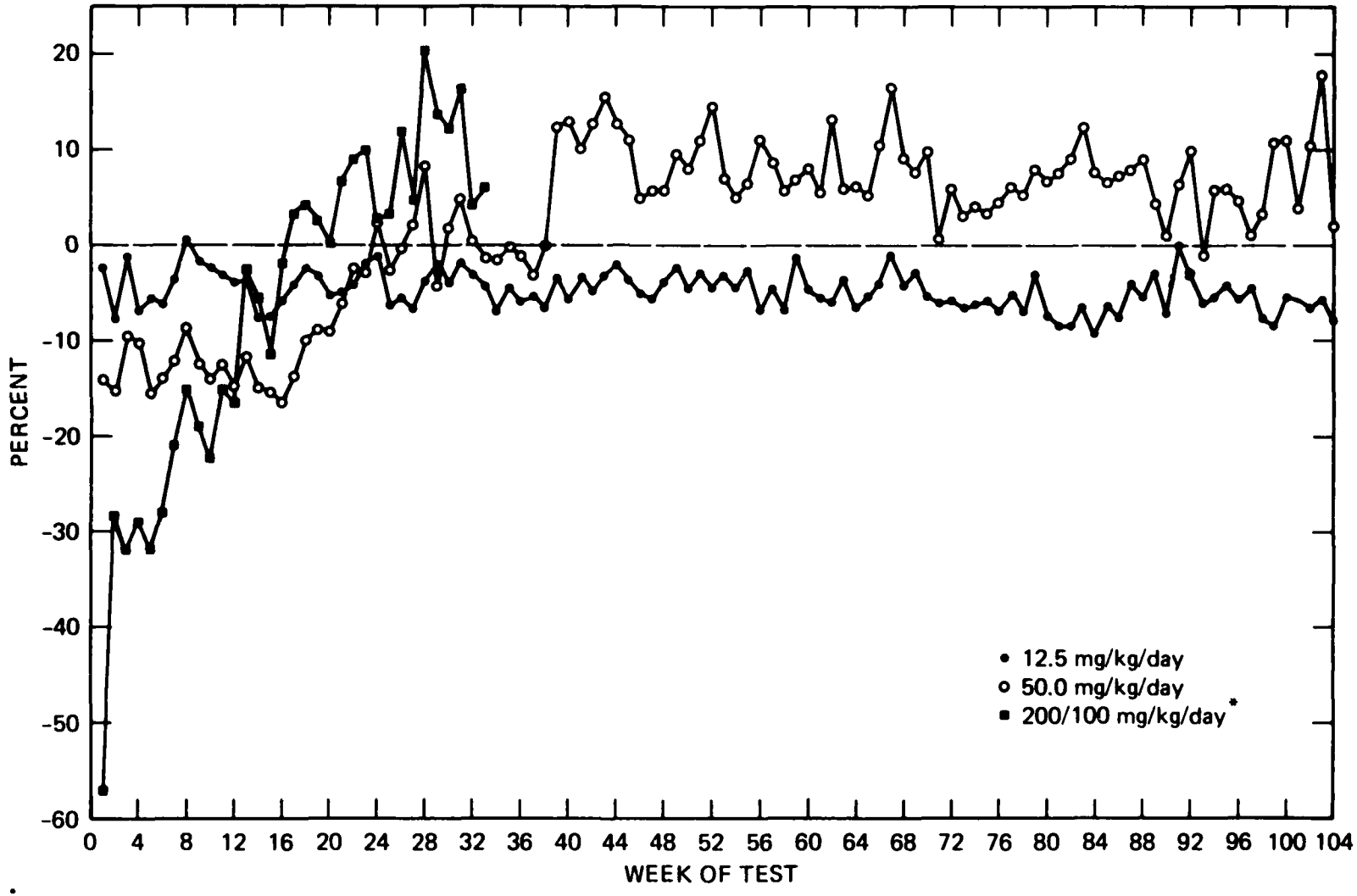
AVERAGE DOSE OF LAP, TNT, AND RDX RECEIVED BY
MALE AND FEMALE RATS TREATED WITH LAP FOR UP TO 2 YEARS

Treatment Level (mg/kg/day)	LAP* (mg/kg/day)	TNT (mg/kg/day)	RDX (mg/kg/day)
	Males		
12.5	12.40 (9.94-13.77)**	7.63 (6.12-8.47)	4.77 (3.82-5.30)
50	50.11 (39.33-57.53)	30.84 (24.20-35.40)	19.27 (15.13-22.13)
200/100†	135.90 (86.77-232.58)	83.63 (53.40-143.13)	52.27 (33.37-89.45)
	Females		
12.5	12.32 (8.74-13.72)	7.58 (5.38-8.44)	4.74 (3.36-5.28)
50	49.83 (35.19-55.10)	30.66 (21.66-33.91)	19.17 (13.53-21.19)
200/100†	135.71 (97.27-233.33)	83.51 (59.86-143.59)	52.20 (37.41-89.74)

* Values given assume that 100% of the compound was available in the diet; based on a TNT/RDX ratio of 1.6 to 1.

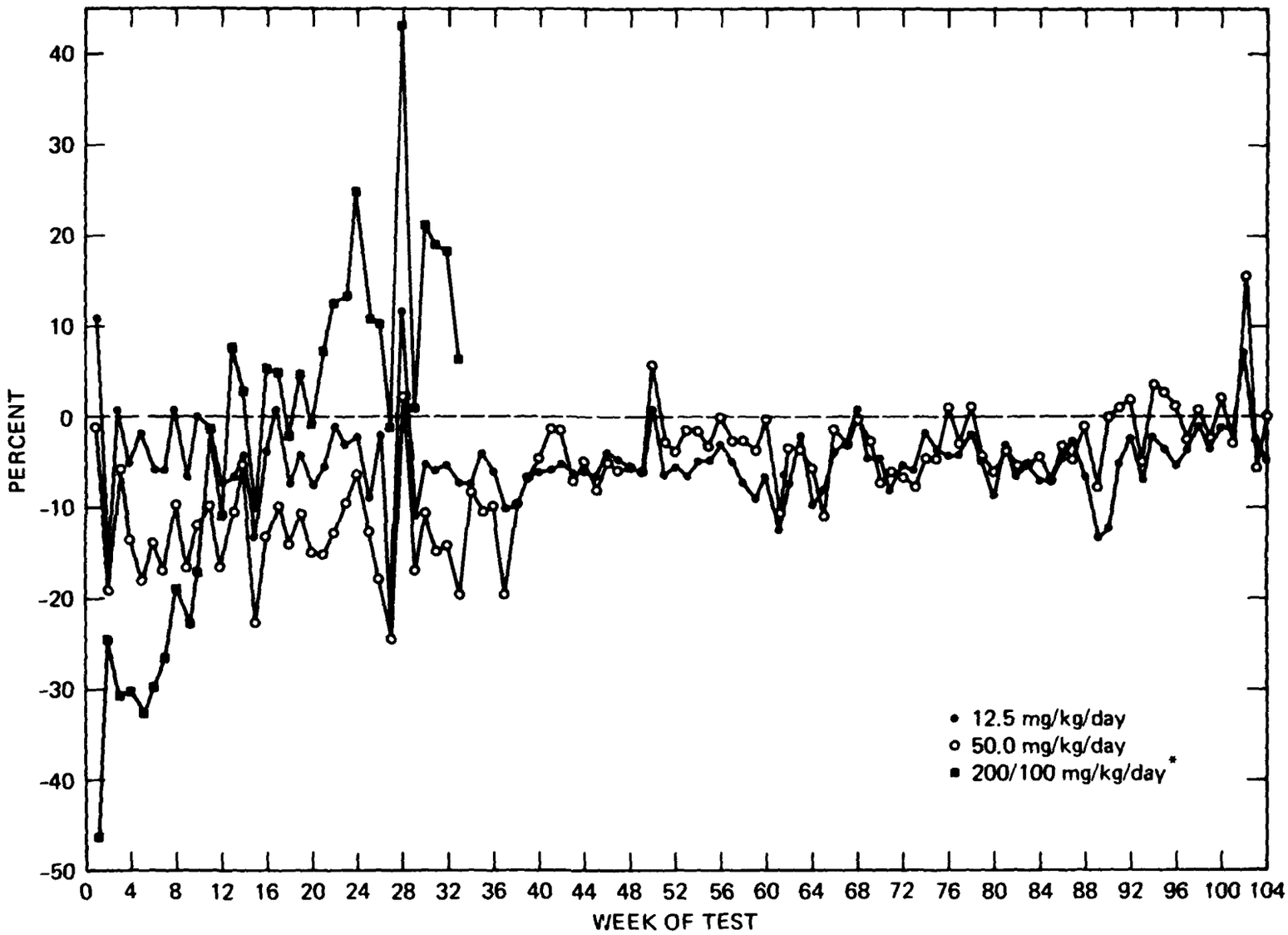
** Parentheses indicate the range of dose received.

† The 200-mg/kg/day dose was reduced to 100 mg/kg/day after 12 weeks; all animals at this dose level were terminated after 33 weeks on test.



*200 mg/kg/day treatment level was reduced to 100 mg/kg/day beginning with the 13th week and terminated after 33 weeks.

FIGURE 4 VARIATION IN FOOD CONSUMPTION RELATIVE TO CONTROL-MALES (%)



*200 mg/kg/day treatment level was reduced to 100 mg/kg/day beginning with the 13th week and terminated after 33 weeks.

FIGURE 5 VARIATION IN FOOD CONSUMPTION RELATIVE TO CONTROL-FEMALES (%)

through 10. Throughout the study, the mid-dose females occasionally consumed more than the controls, significantly so only during Week 102. While food consumption of the low-dose females was generally lower than that of the controls throughout the study, this difference was rarely significant.

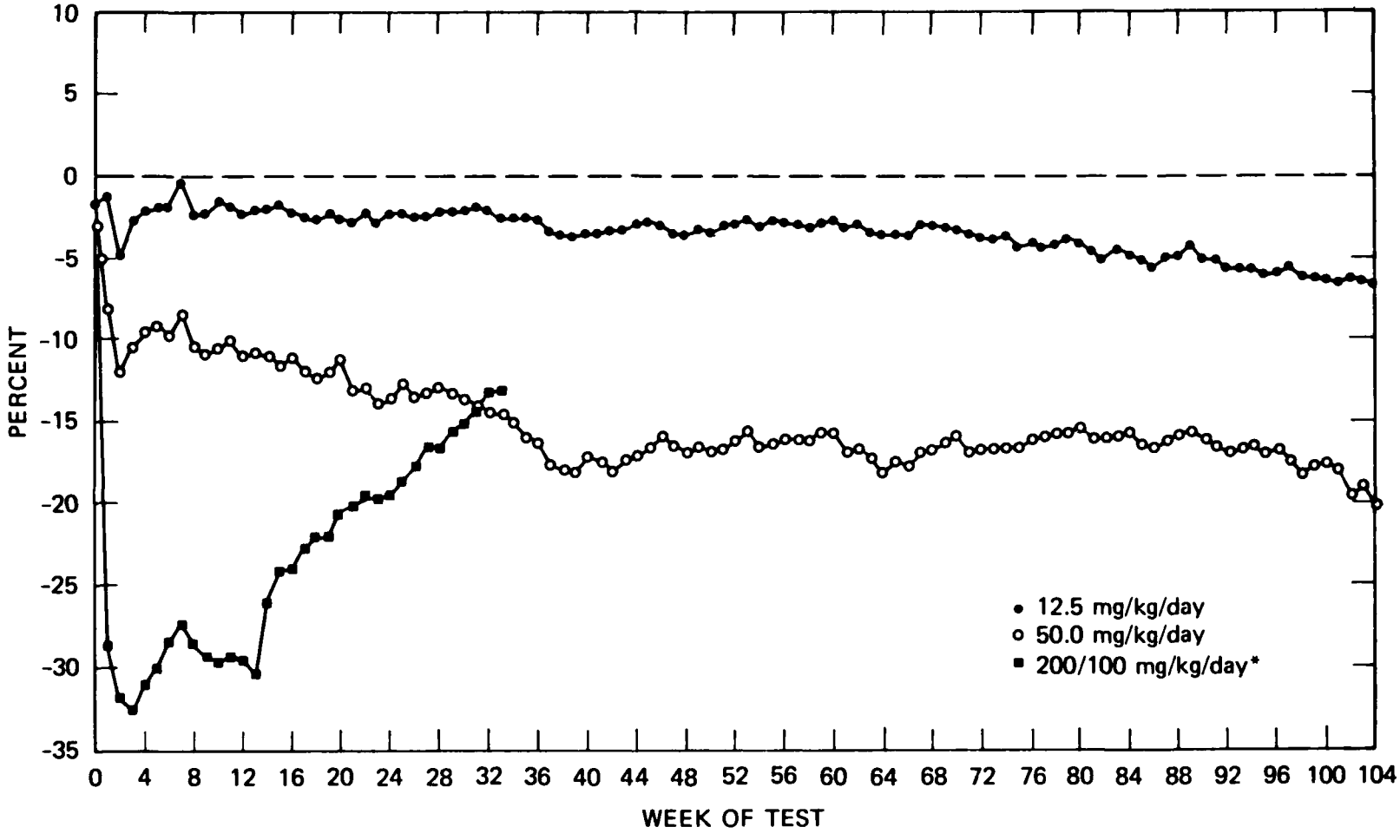
Food consumption in terms of grams of food consumed per kilogram of body weight are presented in Appendices F and G for males and females, respectively. After 1 week of acclimation to the diet, food consumption in the high-dose males increased compared with controls, even when food consumed (g/day) was significantly low (Weeks 1-16). From Week 18, food consumption based on body weight in the mid-dose males exceeded control values; during Weeks 26 through 104, this difference was often significant. Although food consumption per body weight in the low-dose males was usually less than in controls throughout the study, the differences were not significant.

Food consumption based on body weight for the females showed no consistent trends during the first 33 weeks of the study. Females at all three dose levels occasionally showed a statistically significant difference from control values; however, these differences were not consistently in the same direction. At approximately the same time that the high-dose females were sacrificed (Week 34), food consumption based on body weight for the mid-dose females began to increase over that of controls, usually to a significant degree throughout the rest of the study. Beginning with Week 40, an increase was also seen in the low-dose group, although a significant difference was much less frequent.

Body Weights

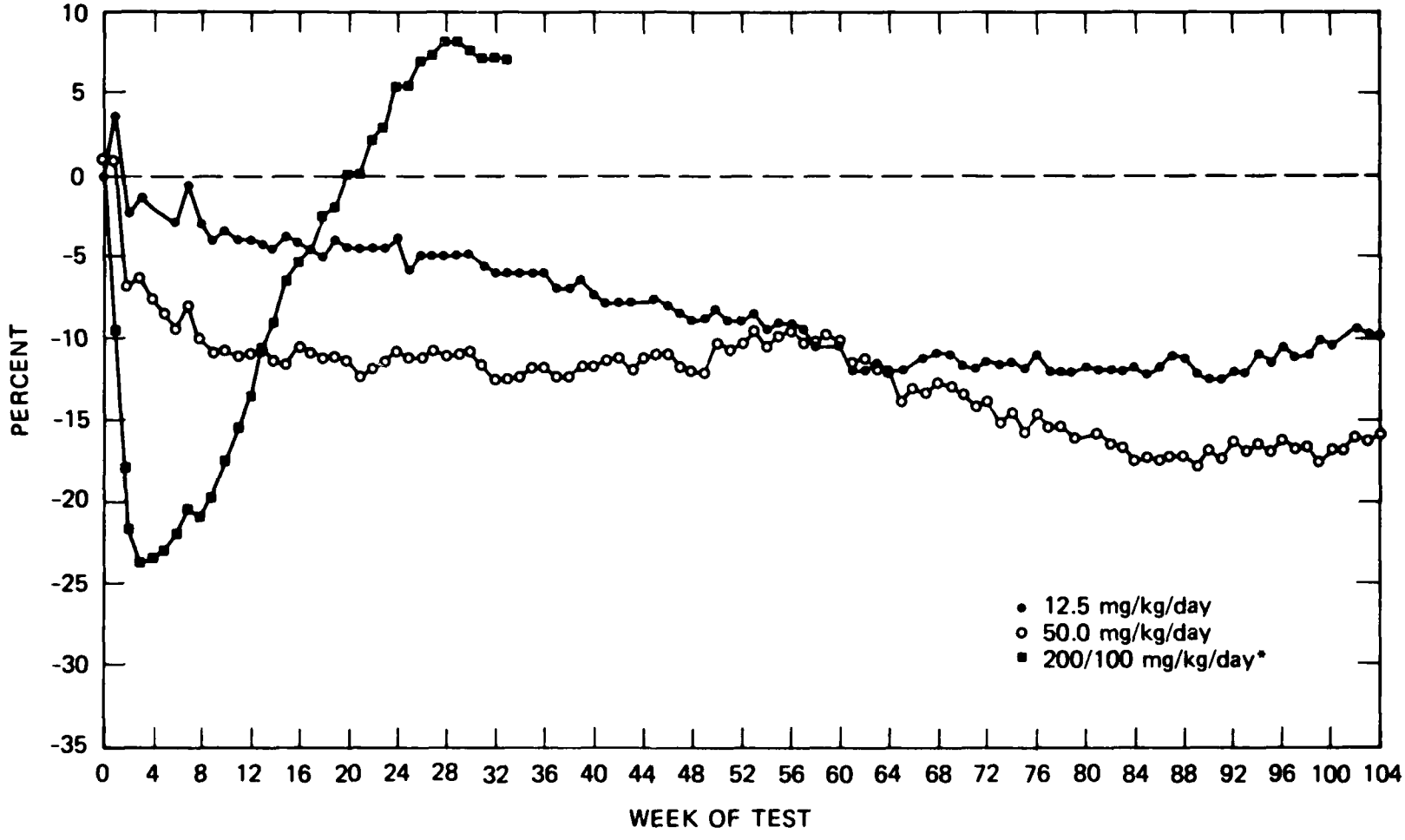
The average weekly body weights for males and females are presented in Appendices H and I, respectively; these data are illustrated in Figures 6 and 7 in terms of percent change in body weight relative to controls. Because the rats were weight-sorted into cages, and cages were randomized into test groups, there is no explanation for the somewhat low initial average body weights for high-dose males compared with controls. After 1 week on test, body weights for the mid- and low-dose groups were also decreased compared with controls; in the mid-dose males these differences were significant. A consistent, statistically significant decrease was also seen in the low-dose males beginning at Week 13. A dose-related response was seen in the body weights for all three dose levels; however, during the last few weeks before the high-dose groups were terminated, the average body weight of the high-dose males began to increase at a faster rate than that of the mid-dose group, exceeding it during Weeks 32 and 33. This increased average weight was due in part to the death of the lighter rats in the high-dose group during this period.

In the females, average body weights showed a dose-related decrease that was significant beginning at Weeks 1, 2, and 5 for the high-, mid-, and low-dose groups, respectively. When the high-dose level was reduced from 200 to 100 mg/kg/day (Week 13), the rats immediately began to gain weight, exceeding first the mid-dose and then the low-dose values. From Week 23 until their termination after 33 weeks on test, the high-dose females weighed significantly more than controls. The low- and mid-dose



*200 mg/kg/day treatment level was reduced to 100 mg/kg/day beginning with the 13th week and terminated after 33 weeks.

FIGURE 6 VARIATION IN BODY WEIGHT RELATIVE TO CONTROL-MALES (%)



*200 mg/kg/day treatment level was reduced to 100 mg/kg/day beginning with the 13th week and terminated after 33 weeks.

FIGURE 7 VARIATION IN BODY WEIGHT RELATIVE TO CONTROL-FEMALES (%)

females continued to weigh significantly less than controls throughout the study.

Weekly body weight gains for males and females are presented in Appendices J and K, respectively. A dramatic decrease in weight gain in the high-dose animals compared with controls was evident through Week 12. When the dose level was reduced from 200 to 100 mg/kg/day, a statistically significant increase in weight gain was seen in these animals compared with controls during Weeks 13 through 15. For the low- and mid-dose males, the main differences in body weight gain compared with controls occurred during the first few months of the study when growth in the control animals was at a maximum and acclimation of the treated groups to the diet greatly reduced their body weight gain. After the first few months, the low-dose animals began to gain weight consistently with the controls; statistically significant differences in both directions were seen occasionally. The mid-dose animals continued to gain less weight than the controls, significantly so at times.

In the females, the initial body weight loss in the high-dose group during the first week of the study was dramatic. Beginning with Week 6, body weight gain began to exceed that of controls, often significantly so. The decrease in body weight gain in the low- and mid-dose groups occurred mainly during the first few months of acclimation. Weight gain fluctuated at all dose levels, and statistically significant changes occurred in both directions.

Clinical Signs and Mortality

Beginning 1 day after the study was initiated and continuing throughout the 104 weeks of the test, the urine of all rats receiving LAP had a reddish coloration. The intensity of the coloration increased with increasing dose. By Week 7, the high-dose males receiving 200 mg/kg/day began to show a low incidence of bloody exudate from the eyes and nose. By the ninth week of the study, this toxic response had occurred in approximately 10% of males and females in the high-dose group. At this time, convulsions and heavy salivation lasting 5 to 15 seconds were observed in a few of these rats. Although both sexes were affected, convulsions occurred more frequently in the males. By the eleventh week of the study, the convulsions were more frequent; approximately 20% of the high-dose males and 10% of the high-dose females had a bloody exudate from the eyes and nose. These males were noted to be aggressive; approximately 10% had abrasions of the face and body, possibly the results of fighting and of impact with the cage and feeders during convulsions. High-dose females appeared to be more excitable than controls or rats at the other levels. By Week 12, seven males at the high-dose level had died or were observed to be moribund and were necropsied, and the high dose was reduced to 100 mg/kg/day for both sexes.

At 100 mg/kg/day, both males and females continued to have convulsions and exhibit aggressive behavior. The incidence of males with abrasions also continued to increase. Thirty percent of the males were affected in this manner by Week 15, and 80% had abrasions by Week 30.

Tables 12 and 13 present the mortality data for males and females, respectively; these data are illustrated in Figures 8 and 9. Of the high-dose males, 50% had died after 26 weeks on test. Because of the excessive toxicity and mortality in the high-dose males, all surviving rats at this dose level were necropsied after 33 weeks. Of the initial 70 rats per sex in the high-dose groups, 19 males and 69 females survived to this termination date.

During Week 29, one male from the mid-dose group was observed to have a convulsion. By Week 30, approximately 30% of the mid-dose males had abrasions on their faces and bodies and were considered to be more aggressive than the controls; the females appeared more excitable than controls when handled. Beginning Week 41, the females in the mid-dose group began to exhibit a low incidence of convulsions. The mid-dose males continued to show abrasions, convulsions, and aggressive behavior throughout the study. An increased mortality rate in the mid-dose males became apparent early in the second year of the study (Table 12, Figure 8). Only 11 of the original males at this level survived the 104 weeks of the study. From Week 89, approximately 70% of the mid-dose males appeared slightly humped and depressed. Mortality in the mid-dose females was not increased compared with the controls; 78% of the rats in this group survived to study termination (Table 13, Figure 9).

Male and female rats at the low-dose level showed no evidence of the convulsions or increased aggression noted in the mid- and high-dose groups, and mortality rates were comparable to controls. Seventy-two and 80% of the control and low-dose males and 75 and 68% of the control and low-dose females, respectively, survived the 104 weeks of study.

Ophthalmic Examination and Histopathology

Initially, the eyes of all rats used in this study were determined to be normal. Table 14 presents a summary of ocular lesions found after 1 year on test. Low incidences of serous or reddish discharge; corneal, lenticular, or lens opacity; and hyperemic scleral or decreased retinal vessels were observed. It is likely that the reddish ocular discharge (chromodacryorrhea), noted more frequently in the females, represents changes in the lacrimal glands rather in the globe itself. These "red tears" may be caused by a variety of factors in rats. Because of the aggressive and excitable behavior of the mid-dose rats, these animals were held more tightly for examination. The effects of physical restraint of the rats during the eye examination is difficult to determine; however, blood flow to the head may have been reduced in the mid-dose rats, thereby affecting the diameter of the retinal vessels. The incidence of all ocular lesions found was too low to determine any dose response.

Tables 15 and 16 present a summary of the results of ocular examinations of male and female rats, respectively, immediately before terminal sacrifice. Corneal dystrophy, anterior Y sutural vacuoles, posterior cortical vacuoles, and conjunctivitis are spontaneous changes that occur in aging rats. Posterior cortical opacity (focal) is a congenital defect associated with the hyaloid membrane.

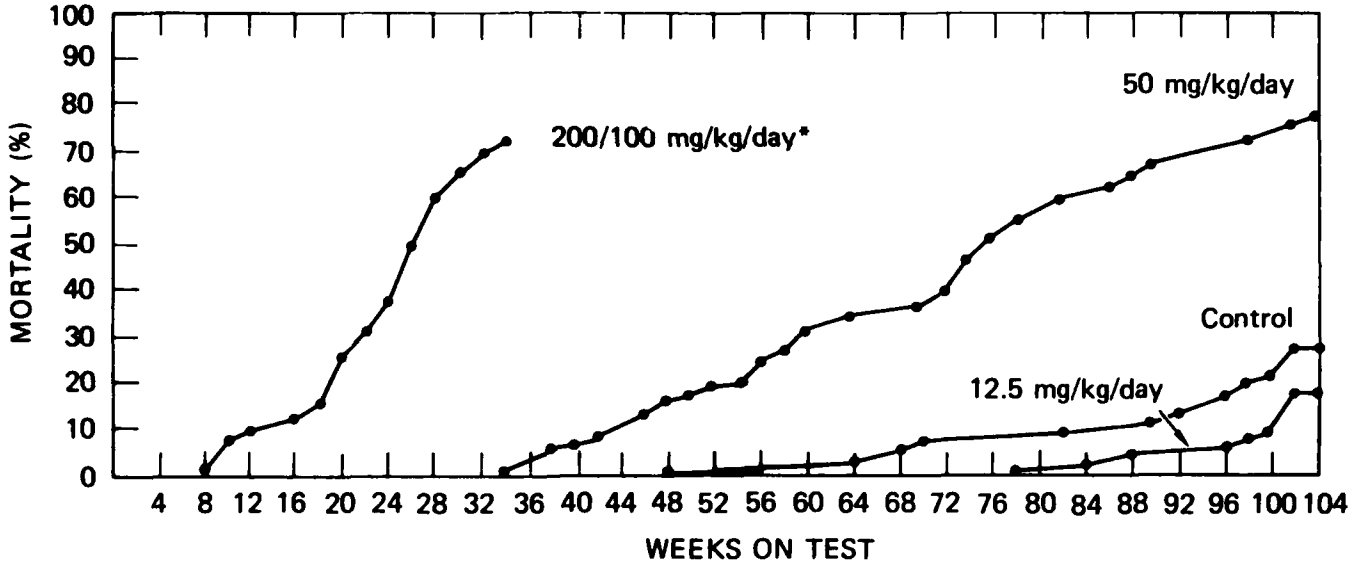
Table 12

MORTALITY OF MALE RATS TREATED WITH LAP

Weeks on Study	Control (65)**	12.5 mg/kg/day (60)	50 mg/kg/day (60)	200/100 mg/kg/day* (60)
0-4	0	0	0	0
5-8	0	0	0	1
9-12	0	0	0	6
13-16	0	0	0	2
17-20	0	0	0	9
21-24	0	0	0	9
25-28	0	0	0	16
29-32	0	0	0	6
33-36	0	0	1	2
37-40	0	0	4	
41-44	0	0	1	
45-48	1	0	4	
49-52	0	0	2	
53-56	0	0	2	
57-60	0	0	4	
61-64	1	0	2	
65-68	2	0	0	
69-72	1	0	3	
73-76	0	0	7	
77-80	0	1	4	
81-84	1	1	1	
85-88	0	1	3	
89-92	3	0	2	
93-96	2	1	0	
97-100	3	2	3	
101-104	4	5	3	
Total Mortality	18 (27.7%)	11 (18.3%)	46 (76.7%)	51 (72.9%)

* Terminated after 33 weeks on test.

** Number of rats in each group (excluding those scheduled for the 12-month interim evaluation).



*At Week 13, the dose level was reduced from 200 to 100 mg/kg/day.
At Week 34, all surviving animals at this dose level were sacrificed.

FIGURE 8 MORTALITY OF MALE RATS TREATED WITH LAP

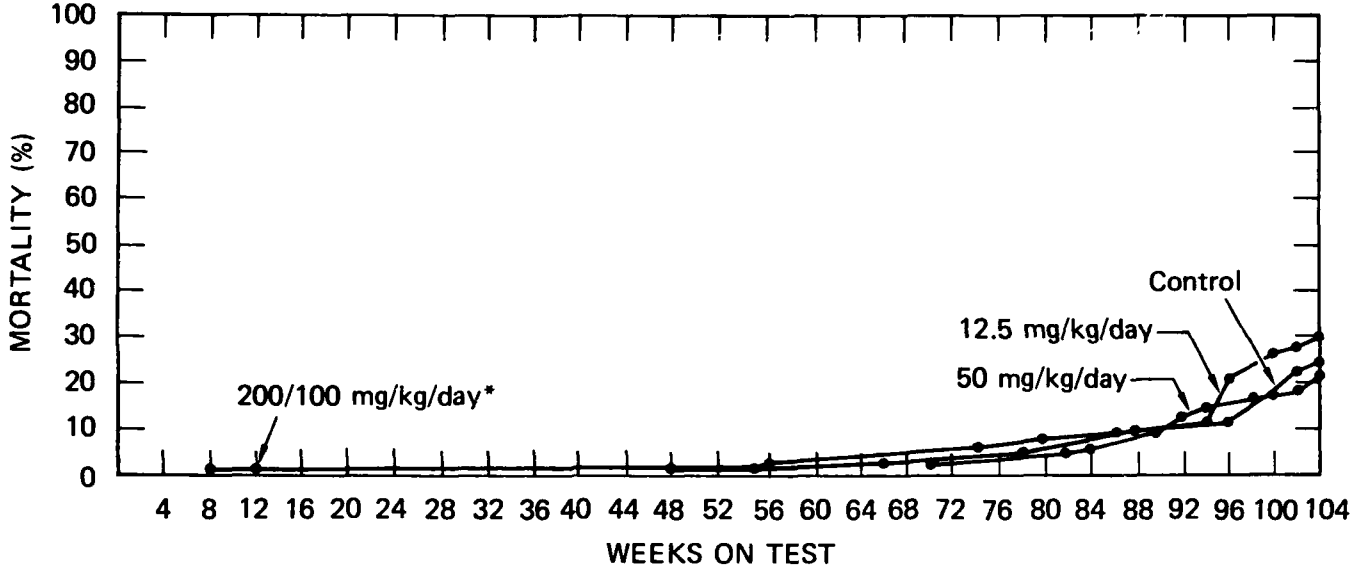
Table 13

MORTALITY OF FEMALE RATS TREATED WITH LAP

Weeks on Study	Control (64)**	12.5 mg/kg/day (60)	50 mg/kg/day (60)	200/100 mg/kg/day* (60)
0-4	0	0	0	0
5-8	0	0	0	0
9-12	0	0	0	1
13-16	0	0	0	0
17-20	0	0	0	0
21-24	0	0	0	0
25-28	0	0	0	0
29-32	0	0	0	0
33-36	0	0	0	0
37-40	0	0	0	
41-44	0	0	0	
45-48	0	1	0	
49-52	0	0	0	
53-56	1	0	0	
57-60	0	0	0	
61-64	0	0	0	
65-68	0	1	0	
69-72	0	0	2	
73-76	2	0	0	
77-80	1	1	0	
81-84	0	2	2	
85-88	1	1	0	
89-92	0	0	4	
93-96	2	7	1	
97-100	4	3	1	
101-104	4	2	3	
Total Mortality	15 (23.4%)	18 (30.0%)	13 (21.7%)	1 (1.4%)

* Terminated after 33 weeks on test.

** Number of rats in each group (excluding those scheduled for the 12-month interim evaluation). One female was also excluded when discovered to be pregnant.



*At Week 13, the dose level was reduced from 200 to 100 mg/kg/day
At Week 34, all surviving animals at this level were sacrificed.

FIGURE 9 MORTALITY OF FEMALE RATS TREATED WITH LAP

Table 14

RESULTS OF OCULAR EXAMINATION OF RATS
TREATED WITH LAP FOR ONE YEAR

Finding	Number of Rats Observed with Ocular Lesions					
	Control		12.5 mg/kg/day		50 mg/kg/day	
	Right	Left	Right	Left	Right	Left
Males:	(64)*		(60)		(47)	
Reddish ocular discharge	0	0	0	0	1	1
Lenticular opacity	0	0	0	0	0	2
Hyperemic scleral vessels	0	0	0	0	1	0
Retinal vessels decreased in diameter	0	0	1	0	2	1
Females:	(64)		(59)		(60)	
Serous ocular discharge	2	1	0	0	0	0
Reddish ocular discharge	2	5	1	3	1	1
Corneal opacity	0	2	0	0	0	0
Lenticular opacity	1	0	1	1	1	1
Lens opacity	0	0	0	1	0	0
Retinal vessels decreased in diameter	0	0	0	0	2	0

*Number of rats examined.

Table 15

RESULTS OF OCULAR EXAMINATION OF MALE RATS
TREATED WITH LAP FOR TWO YEARS

Finding	Number of Rats Observed with Ocular Lesions					
	Control		12.5 mg/kg/day		50 mg/kg/day	
	Right	Left	Right	Left	Right	Left
	(47)*		(49)		(13)	
Normal	2	10	4	3	1	0
Corneal dystrophy	35	28	37	41	6	9
Anterior Y sutural vacuoles	32	22	23	33	0	2
Posterior cortical vacuoles	12	6	8	5	1	1
Conjunctivitis	2	1	3	1	1	1
Anterior cortical opacity	1	1	1	0	1	1
Posterior cortical opacity	4	3	3	1	0	2
Anterior and posterior cortical opacity	1	2	1	1	4	4
Deep anterior chamber	0	1	0	0	3	2
Lens resolution or lens luxation	0	1	0	0	2	1
Complete cataract	1	1	2	0	2	1
Retina blurred	1	1	0	0	0	0
Retina (fundus) blurred	0	0	0	0	1	1
Fundus, cannot visualize	2	2	2	0	5	2
Hyphemia[1]	1	0	1	0	0	0
Phthisis[2]	0	0	0	0	1	0
Lid defect[3]	1	0	0	0	1	2
Keratitis[4]	0	0	0	0	0	2

* Number of rats examined.
1 Anterior chamber filled with blood.
2 Small, missing or dead globe
3 V-shaped defect in lid margin.
4 Vascular proliferation into the cornea.

Table 16

RESULTS OF OCULAR EXAMINATION OF FEMALE RATS
TREATED WITH LAP FOR TWO YEARS

Finding	Number of Rats Observed with Ocular Lesions					
	Control		12.5 mg/kg/day		50 mg/kg/day	
	Right	Left	Right	Left	Right	Left
	(49)*		(42)		(47)	
Normal	4	6	3	4	0	0
Corneal dystrophy	37	36	30	34	18	17
Anterior Y sutural vacuoles	15	9	17	14	5	5
Posterior cortical vacuoles	6	3	7	4	0	0
Conjunctivitis	7	3	3	2	5	2
Anterior cortical opacity	1	2	1	1	4	3
Posterior cortical opacity	6	6	4	4	5	5
Anterior and posterior cortical opacity	6	5	6	4	10	8
Deep anterior chamber	1	0	0	0	26	26
Lens resolution or lens luxation	1	0	0	0	17	18
Complete cataract	2	1	0	1	9	9
Retina blurred	2	2	0	2	2	1
Retina (fundus) blurred	1	1	2	0	1	3
Fundus, cannot visualize	1	1	0	0	14	11
Complete corneal opacity	0	0	0	0	1	1
Extensive posterior cortical opacity	0	2	0	0	0	0
Hyphemia[1]	0	0	0	0	0	2
Phthisis[2]	0	0	0	0	0	1
Lid defect[3]	0	0	1	0	0	0
Keratitis[4]	0	0	0	0	2	1
Sublux medial[5]	0	0	0	0	1	0
Sublux laternal[6]	0	0	0	0	1	1

* Number of rats examined.
1 Anterior chamber filled with blood.
2 Small, missing, or dead globe.
3 V-shaped defect in lid margin.
4 Vascular proliferation into the cornea.
5 Displacement of lens in medial direction.
6 Displacement of lens in lateral direction.

The most consistent ocular defect observed occurred in the lens. Occurrences of anterior cortical opacity, posterior cortical opacity, anterior and posterior cortical opacity, complete cataract, deep anterior chamber, and lens luxation or resolution were observed in both treated and control groups. In all groups (including controls), the occurrence of lens changes was greater in the females. The incidences of these findings were no greater in the low-dose animals than in controls of either sex. The incidence of these ocular defects in the mid-dose animals was 5.2 times higher than in controls in the males and 4.7 times higher in the females.

Tables 17 and 18 summarize the ocular lesions seen during histopathologic evaluation in the male and female rats, respectively, that died during the second year on test or were terminated after completion of 104 weeks. Phthisis bulbi (shrinkage and wasting of the eyeball) was seen in three mid-dose males. This may be a sequela to chemically related eye damage, but it may also be due to an unrelated injury such as trauma. All other biologically significant changes in the mid-dose males--acute inflammation in the anterior chamber, acute inflammation and neovascularization of the cornea, moderate/marked lens degeneration, and multifocal/diffuse retinal degeneration--were treatment-related.[36,37] Age-related changes,[38,39] such as mild focal lens degeneration and mild peripheral retinal degeneration, common in control and low-dose males were usually obliterated in the mid-dose group by more severe toxic changes and early mortality. The decreased incidence of scleral mineralization seen in mid-dose males may be due to early mortality.

In the mid-dose females, the neovascularization of the cornea, moderate/marked lens degeneration, lens mineralization, and multifocal/diffuse retinal degeneration were treatment-related and were statistically and biologically significant.[36,37] Age-related changes[38,39] were common in control and low-dose females but were obliterated by more severe toxic changes in the mid-dose females. The cause and biological significance of decreased focal scleral mineralization is not known.

Hematology

Tables 19 and 20 summarize the hematology and clinical chemistry analyses for animals terminated after one year. In both sexes, a significant increase in WBC and a decrease in RBC, Hgb, and Hct were seen at the mid-dose level (Table 19). The low-dose level showed no effect for these parameters and the differential count did not appear to be affected at any dose level.

Numerous clinical chemistry parameters were also significantly affected in animals at the mid-dose level (Table 20). Phosphorus, however, was the only parameter that was consistently altered (increased) in both sexes at this dose level. Some parameters were significantly affected in both sexes at the low-dose level; however, the direction of the effects and the parameters affected were not consistent.

Summaries of hematology and clinical chemistry analyses for the terminal necropsy are presented in Tables 21 and 22. Numerous statistically significant changes in hematologic parameters in both sexes were seen at the mid-dose level, including an increase in the WBC and a

Table 17

SUMMARY OF MICROSCOPIC OCULAR LESIONS IN MALE RATS
[Dead or Moribund (13-24 Months), and Terminal Necropsy]

Location	Lesion	Number of Lesions		
		Control	12.5 mg/kg/d	50 mg/kg/d
		Percent* (106)**	Percent (96)	Percent (38)
	Phthisis bulbi (shrinkage and wastage of the eyeball)	0 0	0 0	3† 8
Anterior Chamber	Hemorrhage	0 0	0 0	1 3
	Inflammation, acute	0 0	0 0	3† 8
Cornea	Inflammation, acute	0 0	0 0	3† 8
	Inflammation, chronic	0 0	2 2	2 5
	Hyperplasia, epithelial, focal	1 1	1 1	0 0
	Mineralization, focal	1 1	0 0	2 5
	Neovascularization	2 2	0 0	5† 13
Lens	Degeneration, focal mild	52 49	50 52	22 58
	Degeneration, focal moderate/ marked	8 8	1 1	10† 26
	Degeneration, diffuse mild	0 0	0 0	1 3

* Percent based on number of eyes examined.
** Number of eyes examined.
† Statistically significant, $p < 0.05$.

Table 17 (concluded)

Location	Lesion	Number of Lesions		
		Control	12.5 mg/kg/d	50 mg/kg/d
		Percent* (106)**	Percent (96)	Percent (38)
Lens	Degeneration, diffuse moderate/ marked	1 1	0 0	3 8
	Mineralization	6 6	2 2	6 16
Posterior Chamber	Hemorrhage	2 2	0 0	0 0
Retina	Degeneration, peripheral	59 56	44 46	14 37
	Degeneration, multifocal/ diffuse	6 6	5 5	9† 24
Sclera	Hemorrhage, focal	1 1	0 0	0 0
	Inflammation, chronic focal	0 0	0 0	1 3
	Mineralization, focal mild	33 31	30 31	4† 11

Table 18

SUMMARY OF MICROSCOPIC OCULAR LESIONS IN FEMALE RATS
[Dead or Moribund (13-24 Months) and Terminal Necropsy]

Location	Lesion	Number of Lesions		
		Control	12.5 mg/kg/d	50 mg/kg/d
		Percent*	Percent	Percent
		(114)**	(92)	(108)
Anterior Chamber	Inflammation, acute focal	0	0	1
		0	0	0
	Inflammation, chronic focal	1	0	0
		1	0	0
	Proteinaceous debris	0	1	3
		0	1	3
Cornea	Degeneration, focal	0	0	1
		0	0	1
	Hyperplasia, epithelial, focal	1	0	0
		1	0	0
	Inflammation, acute	1	0	1
		1	0	1
	Inflammation, chronic	1	0	3
		1	0	3
	Neovascularization	1	0	11†
		1	0	10
Iris	Inflammation, chronic	0	0	1
		0	0	1
	Hyperplasia, focal mild	0	0	1
		0	0	1
Lens	Degeneration, focal mild	49	42	19†
		43	46	18
	Degeneration, focal moderate/ marked	7	12	53†
		6	13	49

* Percent based on number of eyes examined.
**Number of eyes examined.
† Statistically significant, $p < 0.05$.

Table 18 (concluded)

Location	Lesion	Number of Lesions		
		Control	12.5 mg/kg/d	50 mg/kg/d
		Percent*	Percent	Percent
		(114)**	(92)	(108)
Lens	Degeneration, diffuse, mild	0	1	0
		0	1	0
	Degeneration, diffuse, moderate to marked	3	7	26†
		3	8	24
	Hyperplasia, subcapsule epithelium	0	0	2
		0	0	2
	Mineralization	3	3	55†
		3	3	51
Optic Nerve	Gliosis	0	0	3
		0	0	3
Retina	Degeneration, peripheral	71	58	35†
		62	63	32
	Degeneration, multifocal/ diffuse	21	21	66†
		18	23	61
	Inflammation, acute	1	0	0
		1	0	0
	Leukemia	1	1	0
		1	1	0
Posterior Chamber	Hemorrhage	0	0	1
		0	0	1
Sclera	Mineralization, focal	12	6	1†
		11	7	1

Table 19

HEMATOLOGY ANALYSES OF MALE AND FEMALE RATS
TREATED WITH LAP

(1-Year Necropsy)

Parameter	Males			Females		
	Control (10)*	12.5 mg/kg/day (9)	50 mg/kg/day (8)	Control (10)	12.5 mg/kg/day (10)	50 mg/kg/day (10)
WBC (x 10^3)	4.9 ± 1.1	5.3 ± 1.0	6.2 ± 1.0†	3.0 ± 0.4	3.2 ± 0.6	3.9 ± 1.3†
RBC (x 10^6)	8.68 ± 0.3	8.64 ± 0.1	7.98 ± 0.3*	7.78 ± 0.2	7.60 ± 0.3	6.81 ± 0.7*
Hgb (gm %)	15.1 ± 0.8	14.6 ± 0.3	13.7 ± 0.5*	14.8 ± 0.5	14.5 ± 0.7	12.9 ± 1.3*
Hct (%)	43.2 ± 2.9	41.7 ± 0.8	39.1 ± 1.3*	42.2 ± 1.6	40.7 ± 1.6	36.9 ± 3.6*
MCV (μ^3)	50 ± 1.1	48 ± 0.9	49 ± 2.0	54 ± 1.1	53 ± 1.1	54 ± 1.1
MCH ($\mu\mu g$)	17.2 ± 0.4	16.7 ± 0.3	17.0 ± 0.6	18.8 ± 0.2	18.7 ± 0.3	18.6 ± 0.5
MCHC (%)	34.8 ± 1.0	34.8 ± 0.5	35.0 ± 0.3	34.9 ± 0.5	35.1 ± 0.6	34.6 ± 0.3
Differential (%)	(10)	(10)	(8)	(10)	(10)	(10)
PMN	45 ± 14.4	47 ± 13.2	39 ± 7.6	29 ± 6.8	27 ± 11.9	27 ± 6.8
Bands	0.1 ± 0.3	0.1 ± 0.3	0.0	0.3 ± 0.5	0.1 ± 0.3	0.2 ± 0.4
Lymph	53 ± 14.7	51 ± 13.0	60 ± 8.2	68 ± 6.8	70 ± 12.4	70 ± 6.3
Mono	0.7 ± 0.8	1.5 ± 1.5	1.3 ± 1.3	1.9 ± 1.7	1.8 ± 1.5	1.9 ± 1.3
Eosino	1.2 ± 1.4	0.6 ± 0.7	0.4 ± 1.1	0.6 ± 1.0	0.5 ± 1.0	1.0 ± 0.8
Baso	0.1 ± 0.3	0.0	0.0	0.2 ± 0.6	0.0 ± 0.3	0.0

* Number of rats sampled per treatment level.
† Significant, $p < 0.05$.
* Significant, $p < 0.01$.

Table 20

CLINICAL CHEMISTRY ANALYSES OF MALE AND FEMALE RATS TREATED WITH LAP

(1-Year Necropsy)

Parameter	Males			Females		
	Control (10)*	12.5 mg/kg/day (10)	50 mg/kg/day (8)	Control (10)	12.5 mg/kg/day (10)	50 mg/kg/day (10)
Glucose (mg %)	184 ± 19	189 ± 1.8	157 ± 33†	184 ± 27	194 ± 27	180 ± 23
BUN (mg %)	14 ± 1.0	13 ± 0.9	14 ± 1.1	14 ± 1.7	16 ± 2.8†	17 ± 2.0‡
Creatinine (mg %)	0.5 ± 0.07	0.6 ± 0.07	0.5 ± 0.05	0.5 ± 0.06	0.6 ± 0.08	0.6 ± 0.05
Uric acid (mg %)	2.5 ± 1.0	1.9 ± 0.9	1.2 ± 0.6‡	2.5 ± 0.8	1.7 ± 0.7†	1.8 ± 0.9
Na^+ (meq/L)	146 ± 1.6	147 ± 0.8†	146 ± 1.2	146 ± 2.0	147 ± 1.4	146 ± 0.8
K^+ (meq/L)	5.8 ± 0.9	5.9 ± 0.7	5.5 ± 1.2	5.9 ± 0.9	5.6 ± 0.6	5.9 ± 1.2
CO_2 (meq/L)	28 ± 0.8	28 ± 0.5	31 ± 1.2‡	25 ± 1.4	25 ± 1.6	26 ± 3.0
Cl^- (meq/L)	98 ± 1.8	98 ± 1.4	98 ± 1.2	101 ± 2.3	103 ± 2.4	101 ± 2.3
Calcium (mg %)	10.5 ± 0.3	10.6 ± 0.2	10.4 ± 0.3	11.0 ± 0.4	10.7 ± 0.4	10.7 ± 0.4
Phosphorus (mg %)	4.3 ± 0.3	4.7 ± 0.4†	5.8 ± 0.5‡	3.9 ± 0.5	3.9 ± 0.8	4.9 ± 1.0‡
Balance ($Na-[Cl+CO_2]$)	20 ± 1.3	20 ± 1.6	18 ± 1.9‡	21 ± 3.5	19 ± 2.4	19 ± 1.9
Cholesterol (mg %)	80 ± 7.3	91 ± 14.2†	67 ± 6.3‡	136 ± 15.1	140 ± 19.7	125 ± 15.4
Triglycerides (mg %)	69 ± 16	60 ± 33	25 ± 16‡	46 ± 16	25 ± 9†	41 ± 30
Total bilirubin (mg %)	0.03 ± 0.05	0.05 ± 0.05	0	0.01 ± 0.03	0	0
SGOT (mU/ml)	274 ± 87	280 ± 126	253 ± 164	276 ± 145	388 ± 247	324 ± 217
SGPT (mU/ml)	138 ± 57	140 ± 77	107 ± 79	119 ± 54	170 ± 136	120 ± 61
LDH (mU/ml)	2425 ± 281	2201 ± 456	1815 ± 687‡	1711 ± 550	1632 ± 925	1163 ± 663
Alkaline phosphatase (mU/ml)	167 ± 24	152 ± 23	170 ± 19	129 ± 22	132 ± 34	201 ± 39‡
Total iron (mcg %)	141 ± 15	108 ± 10‡	142 ± 19	274 ± 38	252 ± 55	279 ± 81
Total protein (gm %)	5.9 ± 0.1	6.2 ± 0.2†	6.0 ± 0.3	6.8 ± 0.3	6.8 ± 0.4	6.3 ± 0.2‡
Albumin (gm %)	2.6 ± 0.1	2.7 ± 0.1†	2.6 ± 0.1	3.3 ± 0.2	3.3 ± 0.2	3.0 ± 0.1‡
Globulin (gm %)	3.4 ± 0.1	3.5 ± 0.1	3.4 ± 0.2	3.5 ± 0.1	3.5 ± 0.2	3.4 ± 0.1†
A/G ratio	0.77 ± 0.05	0.78 ± 0.04	0.75 ± 0.08	0.93 ± 0.05	0.92 ± 0.04	0.86 ± 0.05‡

* Number of rats sampled per treatment level.
† Significant, $p < 0.05$.
‡ Significant, $p < 0.01$.

Table 21

HEMATOLOGY ANALYSES OF MALE AND FEMALE RATS
TREATED WITH LAP

(Terminal Necropsy)

Parameter	Males			Females		
	Control (20)*	12.5 mg/kg/day (20)	50 mg/kg/day (18)	Control (20)	12.5 mg/kg/day (20)	50 mg/kg/day (20)
WBC (x 10^3)	9.7 ± 8.8	6.6 ± 1.8	8.1 ± 3.4	4.0 ± 0.6	4.5 ± 1.9	6.2 ± 2.4‡
RBC (x 10^6)	7.74 ± 2.2	8.11 ± 1.1	6.96 ± 1.5	7.17 ± 0.5	6.59 ± 1.2†	6.44 ± 0.8‡
Hgb (gm %)	15.2 ± 3.9	15.0 ± 2.1	12.2 ± 2.3‡	14.3 ± 0.9	13.0 ± 2.0‡	12.1 ± 1.1‡
Hct (%)	41.8 ± 9.2	41.7 ± 5.3	35.2 ± 6.4‡	40.7 ± 4.0	36.8 ± 5.8‡	35.5 ± 3.8‡
MCV (μ^3)	57 ± 10.8	52 ± 1.2	53 ± 12.6	56 ± 1.5	56 ± 4.6	55 ± 3.5
MCH (μμg)	20.1 ± 3.0	18.4 ± 0.5	18.2 ± 4.0†	19.8 ± 0.7	19.7 ± 1.5	18.9 ± 1.3†
MCHC (%)	35.6 ± 1.9	35.6 ± 0.9	34.4 ± 1.1‡	35.5 ± 1.3	35.2 ± 1.1	34.2 ± 1.5‡
Differential (%)	(20)	(20)	(17)	(20)	(20)	(18)
PMN	42 ± 10.0	45 ± 8.4	51 ± 12.1‡	37 ± 7.9	42 ± 9.8	39 ± 10.4
Bands	0.2 ± 0.5	0.2 ± 0.5	0	0.1 ± 0.3	0	0.1 ± 0.2
Lymph	55 ± 10.3	52 ± 8.3	46 ± 12.6‡	60 ± 8.2	56 ± 9.6	59 ± 10.2
Mono	1.3 ± 1.7	2.0 ± 1.5	2.4 ± 3.0	0.9 ± 1.1	1.2 ± 1.3	1.3 ± 1.1
Eosino	1.0 ± 1.0	1.0 ± 1.2	0.4 ± 0.6	1.2 ± 1.1	0.8 ± 1.0	0.4 ± 0.7†
Baso	0	0	0	0	0	0
	(20)	(20)	(13)	(20)	(20)	(20)
Reticulocyte (%)	4.9 ± 7.9	2.6 ± 1.6	3.5 ± 1.5	1.4 ± 0.7	2.3 ± 2.2†	1.9 ± 1.2

* Number of rats sampled per treatment level.
† Significant, $p < 0.05$.
‡ Significant, $p < 0.01$.

Table 22

CLINICAL CHEMISTRY ANALYSES OF MALE AND FEMALE RATS TREATED WITH LAP

(Terminal Necropsy)

Parameter	Males			Females		
	Control (20*)	12.5 mg/kg/day (20)	50 mg/kg/day (18)	Control (20)	12.5 mg/kg/day (20)	50 mg/kg/day (20)
Glucose (mg %)	150 ± 2.9	155 ± 23	163 ± 37	174 ± 24	154 ± 17‡	148 ± 25‡
BUN (mg %)	18 ± 2.8	15 ± 1.7	45 ± 90.1	17 ± 2.1	17 ± 2.4	19 ± 3.6
Creatinine (mg %)	0.7 ± 0.07	0.7 ± 0.08	1.6 ± 3.63	0.6 ± 0.08	0.6 ± 0.06	0.6 ± 0.13
Uric acid (mg %)	2.4 ± 0.7	2.0 ± 0.6	2.0 ± 1.0	2.8 ± 1.0	2.1 ± 0.6‡	2.0 ± 0.6‡
Na^+ (meq/L)	144 ± 1.9	143 ± 1.8	144 ± 2.7	140 ± 1.3	143 ± 2.8†	143 ± 2.0‡
K^+ (meq/L)	5.5 ± 0.6	5.0 ± 0.6	6.1 ± 1.8	5.9 ± 0.9	5.3 ± 0.6‡	5.4 ± 0.7†
CO_2 (meq/L)	26 ± 2.1	27 ± 2.0	28 ± 6.6	22 ± 2.6	25 ± 2.2†	25 ± 5.0†
Cl^- (meq/L)	100 ± 2.4	102 ± 4.4	98 ± 5.2	99 ± 2.0	99 ± 2.8	99 ± 2.6
Calcium (mg %)	10.6 ± 0.3	10.4 ± 0.4	10.4 ± 0.6	10.4 ± 0.5	10.5 ± 0.5	10.4 ± 0.6
Phosphorus (mg %)	4.6 ± 0.8	4.4 ± 0.5	5.9 ± 3.3†	3.7 ± 0.6	3.9 ± 0.7	4.5 ± 1.4†
Balance ($Na-[Cl+CO_2]$)	18 ± 4.0	14 ± 6.0†	18 ± 8.1	19 ± 2.6	20 ± 3.5	20 ± 6.8
Cholesterol (mg %)	118 ± 30	125 ± 71	157 ± 76	120 ± 11	119 ± 19	124 ± 22
Triglycerides (mg %)	169 ± 76	111 ± 41†	161 ± 109	100 ± 38	59 ± 35‡	60 ± 33‡
Total bilirubin (mg %)	0.13 ± 0.19	0.10 ± 0.04	0.29 ± 0.88	0.02 ± 0.04	0.08 ± 0.16†	0.04 ± 0.05
SGOT (mU/ml)	177 ± 68	160 ± 126	203 ± 382	204 ± 74	131 ± 46	184 ± 234
SGPT (mU/ml)	90 ± 37	93 ± 120	72 ± 49	108 ± 39	69 ± 13	97 ± 143
LDH (mU/ml)	2228 ± 757	1717 ± 535‡	850 ± 372‡	1486 ± 505	946 ± 463‡	960 ± 668‡
Alkaline phosphatase (mU/ml)	245 ± 65	217 ± 30	235 ± 108	247 ± 40	267 ± 50	269 ± 39
Total iron (mcg %)	210 ± 63	181 ± 26	129 ± 41‡	322 ± 43	247 ± 50‡	216 ± 34‡
Total protein (gm %)	6.0 ± 0.3	6.3 ± 0.4	5.6 ± 1.2	6.7 ± 0.3	6.6 ± 0.4	6.6 ± 0.5
Albumin (gm %)	2.6 ± 0.2	2.7 ± 0.2	2.3 ± 0.6‡	3.1 ± 0.1	3.0 ± 0.3	2.9 ± 0.2†
Globulin (gm %)	3.4 ± 0.3	3.7 ± 0.4	3.3 ± 0.7	3.6 ± 0.2	3.6 ± 0.2	3.7 ± 0.3
A/G ratio	0.77 ± 0.09	0.75 ± 0.11	0.68 ± 0.12†	0.88 ± 0.06	0.83 ± 0.07†	0.78 ± 0.07‡

* Number of rats sampled per treatment level.
† Significant, $p < 0.05$.
‡ Significant, $p < 0.01$.

decrease in the RBC in females (seen in both sexes at the one-year sacrifice) and decreases in Hgb, Hct, MCH, and MCHC in both sexes. Females at the low-dose level had slightly less pronounced decreases in the RBC, Hgb, and Hct; no effects were observed at this level in the males. The differential counts in mid-dose males showed a significantly increased percentage of PMNs and a decreased percentage of lymphocytes; females in the mid- and low-dose groups had a decreased percentage of eosinophils and an increased percentage of reticulocytes, respectively.

Few statistically significant differences were seen in the clinical chemistry parameters of treated males. A significant increase in phosphorus and decreases in LDH, total iron, albumin, and the A/G ratio were seen in the mid-dose group. Relatively large increases in a few other parameters such as BUN, creatinine, and potassium reflected kidney damage in the mid-dose males; however, they were not statistically cited because of one rat in the mid-dose group with extensive kidney damage, which greatly inflated the variance in these parameters. Decreases in LDH, electrolyte balance, and triglycerides were seen in males at the low-dose level. This strengthens the significance of the decrease in these parameters in males at the mid-dose level at the one-year necropsy.

Unlike the males, numerous statistically significant changes were seen in low- and mid-dose females at the terminal necropsy. Glucose, uric acid, potassium, triglycerides, LDH, total iron, albumin, and the A/G ratio were significantly decreased at both dose levels, Na^+ and CO_2 were increased. Phosphorus levels were significantly high at the mid-dose level only; albumin was decreased. The total bilirubin was increased only at the low-dose level.

In summary, results of the analyses of the hematology parameters indicated that LAP had an effect on both the myelocytic and erythrocytic series in both males and females at the 50-mg/kg level, and a slight effect (decrease) on the red blood cell parameters in females treated with 12.5 mg/kg. Clinical chemistry parameters for the males at the 50 mg/kg level reflect kidney lesions seen histologically, but do not accurately express the degree of tissue damage.[38,40,41] In the males, only the LDH showed a dose-response, affecting the 12.5 mg/kg level as well as the high dose; a clear dose-response was seen in numerous parameters for the females.

Organ Weights

Tables 23 through 25 present the final average body and organ weights and organ weight ratios for male rats at the one-year necropsy, terminal necropsy, and for those found dead or moribund, respectively. Table 26 presents average body and organ weights and organ weight ratios for the high-dose males and females terminated after 33 weeks on test; these data were not statistically compared with any other group because of the early necropsy date. A statistically significant treatment-related decrease in body weights was seen at the mid-dose level for the one-year necropsy, and at both the low- and mid-dose levels for the terminal necropsy and for rats found dead or moribund. The excessively low body weight of the high dose males that were found dead or moribund was believed to be influenced by the large number of very early deaths in that group. At the one-year necropsy, the kidney weight of the low-dose group was significantly increased

Table 23

AVERAGE BODY WEIGHTS, ORGAN WEIGHTS, AND WEIGHT RATIOS
OF MALE RATS TREATED WITH LAP

(1-Year Necropsy)

	Dose	Weight (g) Body	Brain	Heart	Liver	Spleen	Kidney	Testes
	Control	460	2.21	1.16	13.15	0.71	2.67	3.23
	12.5 mg/kg	443	2.23	1.20	13.79	0.76	2.91†	3.26
	50 mg/kg	375‡	2.29	1.16	13.53	0.69	2.89	2.91
		(8)*	(8)	(8)	(8)	(8)	(8)	(8)
Organ/Body Weight Ratio (g/100 g of body weight)	Control		0.48	0.25	2.86	0.16	0.58	0.70
	12.5 mg/kg		0.51	0.27‡	3.11‡	0.17	0.66‡	0.74
			(9)					
	50 mg/kg		0.61‡	0.31‡	3.60‡	0.18†	0.78‡	0.78
			(8)	(8)	(8)	(8)	(8)	(8)
Organ/Brain Weight Ratio	Control			0.52	5.95	0.32	1.21	1.46
	12.5 mg/kg			0.54	6.21	0.35	1.30	1.46
				(9)	(9)	(9)	(9)	(9)
	50 mg/kg			0.51	5.92	0.30	1.26	1.27†
				(8)	(8)	(8)	(8)	(8)

* Number of animals sampled in parentheses if different from 10.
† $p < 0.05$.
‡ $p < 0.01$.

Table 24

AVERAGE BODY WEIGHTS, ORGAN WEIGHTS, AND WEIGHT RATIOS
OF MALE RATS TREATED WITH LAP

(Terminal Necropsy)

	Dose	Weight (g) Body	Brain	Heart	Liver	Spleen	Kidney	Testes
	Control	456	2.28 (46)*	1.20	15.43	1.59	3.04	5.82
	12.5 mg/kg	432‡	2.29	1.23	16.03 (47)	1.41	3.23‡	5.93
	50 mg/kg	374‡	2.19‡	1.16	18.01‡	1.04	3.34†	6.72
Organ/Body Weight Ratio (g/100 g of body weight)	Control		0.50 (46)	0.26	3.38	0.35	0.67	1.27
	12.5 mg/kg		0.53‡	0.29‡	3.71† (47)	0.33	0.75‡	1.37
	50 mg/kg		0.58‡	0.31‡	4.83	0.28	0.90‡	1.80‡
Organ/Brain Weight Ratio	Control			0.53 (46)	6.81 (46)	0.70 (46)	1.33 (46)	2.56 (46)
	12.5 mg/kg			0.54	7.01	0.62	1.41‡	2.60
	50 mg/kg			0.53	8.28‡	0.48	1.54‡	3.11

* Number of animals sampled in parentheses if different from 47 control, 48 low-dose, and 11 mid-dose rats that were included in the terminal necropsy.
† $p < 0.05$.
‡ $p < 0.01$.

Table 25

AVERAGE BODY WEIGHTS, ORGAN WEIGHTS, AND WEIGHT RATIOS
OF MALE RATS TREATED WITH LAP

(Found Dead or Moribund)

		Weight (g)						
	Dose	Body	Brain	Heart	Liver	Spleen	Kidney	Testes
	Control	420	2.34	1.33	15.68	4.06	3.03	3.43 (17)
	12.5 mg/kg	366‡	2.31	1.46 (11)*	13.86	3.22	3.13	3.41 (11)
	50 mg/kg	370‡	2.33 (45)	1.43 (45)	15.78 (45)	0.86‡ (45)	4.27‡ (43)	2.76 (45)
	200/100 mg/kg	258‡	2.14‡ (43)	1.13‡	11.23‡ (44)	0.51‡	2.84	2.40‡ (44)
Organ/Body Weight Ratio (g/100 g of body weight)	Control		0.57	0.33	0.38	0.99	0.74	0.80 (17)
	12.5 mg/kg		0.63	0.40† (11)	0.38	0.92	0.86	0.93 (11)
	50 mg/kg		0.63 (45)	0.39† (45)	0.42 (45)	0.23‡ (45)	1.15‡ (43)	0.76 (45)
	200/100 mg/kg		0.84‡ (43)	0.44‡	0.44 (44)	0.21‡	1.09‡	0.95 (44)
Organ/Brain Weight Ratio	Control			0.57	6.66	1.70	1.30	1.46 (17)
	12.5 mg/kg			0.56 (11)	6.00	1.37	1.36	1.49 (11)
	50 mg/kg			0.59 (45)	6.76 (45)	0.37‡ (45)	1.82‡ (43)	1.19 (45)
	200/100 mg/kg			0.53 (43)	5.32† (42)	0.24‡ (43)	1.35 (43)	1.15† (42)

* Number of rats sampled in parentheses if different from 18 control, 12 low-dose, 46 mid-dose, and 45 high-dose rats that were found dead or moribund.
† $p < 0.05$.
‡ $p < 0.01$.

Table 26

AVERAGE BODY WEIGHTS, ORGAN WEIGHTS, AND WEIGHT RATIOS
OF MALE AND FEMALE RATS TREATED WITH 200/100 mg/kg/day OF LAP

(Terminal Necropsy After 33 Weeks)

Sex		Weight (g)						
		Body	Brain	Heart	Liver	Spleen	Kidney	Testes
Male		362	2.26	1.09 (18)*	17.16	0.81	2.95	3.11
	Organ/Body Weight Ratio (g/100 g of body weight)		0.6	0.3 (18)	4.7	0.2	0.8	0.9
	Organ/Brain Weight Ratio			0.48 (18)	7.61	0.35	1.29	1.38
Female		232	2.12	0.77	10.19	0.68	1.73	
	Organ/Body Weight Ratio (g/100 g of body weight)		0.9	0.3	4.4	0.3	0.7	
	Organ/Brain Weight Ratio			0.36	4.81	0.32	0.82	

* Number of animals in parentheses if different from 19 males and 69 females that were included in the terminal necropsy.

compared with controls. A significant treatment-related increase in kidney weight was also seen in both the low- and mid-dose males at the terminal necropsy and at the mid-dose level for males found dead or moribund. At the terminal necropsy, the mid-dose group also showed a small but significant decrease in brain weight and an increase in liver weight. The increased liver weight may reflect the induction of liver enzymes to metabolize LAP.[42] In addition to the increased kidney weight in mid-dose males found dead or moribund, this group also showed a significant decrease in spleen weight. Several factors may have contributed to this, including (1) the large number of young, lighter weight, leukemia-free, mid-dose animals that died early in the study, and (2) a lymphoid depletion seen microscopically.

The significant increases in the organ-to-body weight ratios of the various organs measured in at least one of the treated groups--the brain, heart, liver, spleen and kidney--at the one-year necropsy, the brain, heart, liver, kidney, and testes at the terminal necropsy, and the brain, heart, spleen, and kidney in males found dead or moribund--may be due to the treatment-related decrease in body weight in these groups. The treatment-related kidney and liver weight increases discussed previously add to the increase in organ-to-body weight ratio for these organs. The decreased spleen-to-body weight ratio seen in the mid- and high-dose males found dead or moribund is also partly a reflection of the decreased spleen weight in those groups, as previously discussed.

At the 1-year necropsy (Table 23), the only significant change in the organ-to-brain weight ratios was a decrease in the testes-to-brain weight ratio at the mid-dose level. This appears to have resulted from a slightly increased brain weight and a slightly decreased testes weight. At the terminal necropsy (Table 24), a significantly increased organ-to-brain weight ratio was seen for the liver (mid-dose only) and kidneys (low- and mid-doses), probably reflecting an induction of liver enzymes to metabolize LAP and treatment-related kidney damage, as previously discussed. The increased kidney-to-brain weight ratio was also apparent in the mid-dose males found dead or moribund (Table 25). A significantly decreased spleen-to-brain weight ratio was seen at the mid-dose level in rats found dead or moribund, reflecting the decreased spleen weight in this group previously discussed. The significant decrease in organ-to-brain weight ratios for the liver, spleen, and testes seen in the high-dose males that were found dead or moribund reflects a comparison between this group of animals that died within the first 33 weeks of the study, and the death of controls late in the study with a higher incidence of both leukemia and testicular tumors common to aging Fisher-344 rats.[43,44]

Tables 27 through 29 present the final average body and organ weights and organ weight ratios for female rats at the one-year necropsy, terminal necropsy, and for those found dead or moribund, respectively. Average body and organ weights and organ weight ratios for the high-dose females terminated after 33 weeks on test were presented in Table 26. A statistically significant, treatment-related decrease in body weight in the low- and mid-dose levels were seen in females throughout all stages of the study. Females at the mid-dose level at the one-year necropsy showed increased brain and liver weights compared with controls. The increased liver weight (also seen in the males) may have resulted from the induction of liver

Table 27

AVERAGE BODY WEIGHTS, ORGAN WEIGHTS, AND WEIGHT RATIOS
OF FEMALE RATS TREATED WITH LAP*

(1-Year Necropsy)

	Dose	Weight (g) Body	Brain	Heart	Liver	Spleen	Kidney
	Control	240	1.99	0.70	7.08	0.46	1.53
	12.5 mg/kg	211‡	2.01	0.74	6.56	0.42	1.48
	50 mg/kg	207‡	2.10‡	0.71	8.17‡	0.50	1.57
Organ/Body Weight Ratio (g/100 g of body weight)	Control		0.83	0.29	2.95	0.19	0.64
	12.5 mg/kg		0.95‡	0.35‡	3.11	0.20	0.70†
	50 mg/kg		1.03‡	0.35‡	3.95‡	0.24‡	0.76‡
Organ/Brain Weight Ratio	Control			0.35	3.56	0.23	0.77
	12.5 mg/kg			0.37	3.27†	0.21†	0.74
	50 mg/kg			0.34	3.87†	0.23	0.75

* Ten rats sampled per dose level.
† $p < 0.05$.
‡ $p < 0.01$.

Table 28

AVERAGE BODY WEIGHTS, ORGAN WEIGHTS, AND WEIGHT RATIOS
OF FEMALE RATS TREATED WITH LAP

(Terminal Necropsy)

		Weight (g)					
	Dose	Body	Brain	Heart	Liver	Spleen	Kidney
	Control	301	2.04 (48)*	0.86	9.81	1.08	2.00
	12.5 mg/kg	269‡	2.05	0.85	9.69	0.89 (40)	2.00
	50 mg/kg	258‡	2.10‡	0.86	10.39	0.72	2.05
Organ/Body Weight Ratio (g/100 g of body weight)	Control		0.69 (48)	0.29	3.27	0.39	0.67
	12.5 mg/kg		0.77‡	0.32‡	3.62‡	0.33 (40)	0.75‡
	50 mg/kg		0.82‡	0.34‡	4.04‡	0.28	0.80‡
Organ/Brain Weight Ratio	Control			0.43 (48)	4.81 (48)	0.54 (48)	0.98 (48)
	12.5 mg/kg			0.42	4.73	0.44	0.98
	50 mg/kg			0.42	4.96	0.44	0.98

* Number of animals in parentheses if different from 49 control, 41 low-dose, and 47 mid-dose rats that were included in the terminal necropsy.
† $p < 0.05$.
‡ $p < 0.01$.

Table 29

AVERAGE BODY WEIGHTS, ORGAN WEIGHTS, AND WEIGHT RATIOS
OF FEMALE RATS TREATED WITH LAP

(Found Dead or Moribund)

	Dose	Weight (g) Body	Brain	Heart	Liver	Spleen	Kidney
	Control	269	2.06	0.89	10.33	1.82	2.00
	12.5 mg/kg	242	2.13	0.90	9.72	2.01	1.95
	50 mg/kg	223†	2.14	0.77†	8.99	1.14 (12)*	2.23
	200/100 mg/kg	130‡	1.99	0.74	9.78	0.38	1.70
Organ/Body Weight Ratio (g/100 g of body weight)	Control		0.79	0.34	0.39	0.53	0.76
	12.5 mg/kg		0.91†	0.39	0.41	0.94	0.84
	50 mg/kg		0.99‡	0.35	0.40	0.50 (12)	1.01†
	200/100 mg/kg		1.53‡	0.57‡	0.72†	0.29	1.31
Organ/Brain Weight Ratio	Control			0.43	5.00	0.88	0.97
	12.5 mg/kg			0.42	4.56	0.95	0.92
	50 mg/kg			0.36‡	4.26	0.53 (12)	1.05
	200/100 mg/kg			0.37	4.91	0.19	0.85

* Number of animals sampled in parentheses if different from 15 control, 19 low-dose, 13 mid-dose, and 1 high-dose rats that were found dead or moribund.
† $p < 0.05$.
‡ $p < 0.01$.

enzymes to metabolize LAP. A small increase in brain weight was also seen at the mid-dose level in females at the terminal necropsy; conversely, a small decrease in brain weight was seen in the mid-dose males at terminal necropsy. A small but statistically significant decrease was seen in the heart weight of the mid-dose females found dead or moribund.

Significantly increased organ-to-body weight ratios were seen in at least one treated female group for the brain, heart, liver, spleen, and kidney at the one-year necropsy, and for these same organs except the spleen at the terminal necropsy and in rats found dead or moribund. This is mainly due to the treatment-related decrease in body weight, except perhaps in the cases of the increased brain and liver weights previously discussed.

A significant increase in the liver-to-brain weight ratio was seen in the mid-dose females at the one-year necropsy (Table 27), reflecting the increased liver weight in this group. A significant decrease in the liver-to-brain weight ratio was seen in the low-dose group resulting from a slight decrease in the liver weight, and a small decrease in the spleen-to-brain weight ratio, reflecting the small increase in brain weight and decreased spleen weight in this group. No changes were seen in the organ-to-brain weight ratios for females at the terminal necropsy (Table 28). A significant decrease in the heart-to-brain weight ratio was seen in the mid-dose females that were found dead or moribund, reflecting the decreased heart weight previously discussed (Table 29).

In summary, significant findings reflecting treatment-related changes in body weights and relative organ weights included (1) a decrease in body weight with increasing dose in both sexes, (2) an increase in liver weight with increasing dose in males for all three time periods, and in mid-dose females at the terminal necropsy, thought to be influenced by the induction of hepatic enzymes to metabolize LAP, and (3) an increase in kidney weight with increasing dose in males, reflecting treatment-related kidney damage. Although no statistical comparisons were made, examination of the results of the data from the high-dose females terminated at 34 weeks on test (Table 26), which is most appropriately compared with the one-year necropsy data, generally appears to support these conclusions.

Histopathology

Tables 30 and 31 summarize the incidence of tumors with a frequency of at least 5% in each group for all male and female rats examined histologically. No tumors were found in rats at the high-dose level; however, these animals were terminated after only 33 weeks on test. The decreased incidence of anterior pituitary adenomas and interstitial cell tumors of the testes in the mid-dose males is attributable to the early deaths in this group, since the incidence of these tumors usually increases with age.[43-46] In the females, a decreased incidence of mammary gland fibroadenomas and pituitary adenomas was seen at both the low- and mid-dose levels and is believed to be treatment-related. (Anterior pituitary tumors are associated with the occurrence of fibroadenomas of the mammary gland[36] since the former often produce mammotropic hormones.[45])

Table 30

INCIDENCE OF TUMORS IN MALE RATS TREATED WITH LAP

Organ	Tumor	Number of Tumors* Control Percent (75)**	12.5 mg/kg/d Percent (70)	50 mg/kg/d Percent (63)†
Adrenal, medulla	Adenoma	4 5	7 10	2 6
Bone marrow	Leukemia	10 13	5 7	3 5
Heart	Leukemia	4 5	2 3	0
Kidney	Leukemia	4 5	1 1	2 3
Liver	Leukemia	9 12	2 3	4 6
Lung	Leukemia	7 9	4 6	1 2
Lymph nodes, mesenteric	Leukemia	5 7	1 1	1 2
Preputial gland	Adenocarcinoma	1 1	3 5	2 3
Pituitary, anterior	Adenoma	16 21	18 26	3≠ 5
	Carcinoma	3 4	5 7	1 2

* Includes only tumors occurring with a frequency of 5% or less in each group. No tumors were found at the 200/100-mg/kg/day dose level, which was terminated after 33 weeks on test.

** Number of animals in group.

† The tissues of 7 rats at the 50 mg/kg/day dose level were lost to cannibalization.

≠ Significantly less than control ($p < 0.05$).

Table 30 (Concluded)

Organ	Tumor	Number of Tumors		
		Control Percent (75)	12.5 mg/kg/d Percent (70)	50 mg/kg/d Percent (63)
Spleen	Leukemia	12 16	9 13	5 8
Stomach, glandular	Leukemia	4 5	0	0
Testes	Interstitial cell tumor	53 71	56 80	25‡ 40
Thymus	Leukemia	4 5	2 3	2 3
Thyroid	Carcinoma, C-cell	5 7	9 13	2 3

Table 31

INCIDENCE OF TUMORS IN FEMALE RATS TREATED WITH LAP

Organ	Tumor	Number of Tumors* Control Percent (74)**†	12.5 mg/kg/d Percent (70)	50 mg/kg/d Percent (70)
Adrenal	Leukemia	4 5	3 4	1 1
Bone marrow	Leukemia	5 7	9 13	6 9
Kidney	Leukemia	4 5	1 1	2 3
Liver	Leukemia	7 9	7 10	3 4
Lung	Leukemia	4 5	6 9	2 3
Lymph nodes, mesenteric	Leukemia	3 4	5 7	1 1
Mammary gland	Fibroadenoma	20 27	6‡ 9	2‡ 3
Pituitary	Adenoma	31 42	10‡ 14	15‡ 21
	Carcinoma	4 5	4 6	0

* Includes only tumors occurring with a frequency of 5% or less in each group. No tumors were found at the 200/100-mg/kg/day dose level, which was terminated after 33 weeks on test.

** Number of animals in group.

† One control rat was removed from the study when discovered to be pregnant.

‡ Significantly less than control ($p < 0.05$).

Table 31 (Concluded)

Organ	Tumor	Number of Tumors		
		Control Percent (74)	12.5 mg/kg/d Percent (70)	50 mg/kg/d Percent (70)
Spleen	Leukemia	14 19	19 27	10 14
Thyroid	Carcinoma, C-cell	3 4	3 4	5 7
Uterus	Stromal polyp	21 28	14 20	17 24
	Stromal sarcoma	2 3	4 6	3 4

Table 32

SUMMARY OF MICROSCOPIC LESIONS IN HIGH-DOSE (200/100 mg/kg/d) MALE RATS
(Dead or Moribund, 1-33 Weeks)

Organ	Lesion	Number of Lesions 200/100 mg/kg/d Percent (32)*
Adrenal		
Cortex	Degeneration	4 13
Aorta	Mineralization, focal	3 9
Bone	No lesions observed	
Bone Marrow	No lesions observed	
Brain	Hemorrhage, focal	1 3
Diaphragm	Inflammation, acute focal	2 6
	Inflammation, chronic focal	1 3
Esophagus	Hemorrhage, focal	1 3
Heart	Inflammation, chronic focal	3 9
	Inflammation, purulent	1 3
	Mineralization, focal	2 6
	Necrosis, focal	1 3

* Number of animals in group.

Table 32 (continued)

Organ	Lesion	Number of Lesions 200/100 mg/kg/d Percent (32)*
Intestine		
Cecum	Inflammation, acute	1 3
	Mineralization, focal	1 3
	Necrosis, focal	1 3
	Parasitism	1 3
Colon	Inflammation, chronic	1 3
	Parasitism	5 16
Duodenum	No lesions observed	
Ileum	No lesions observed	
Jejunum	No lesions observed	
Kidney	Inflammation, chronic	5 16
	Inflammation, acute	2 6
	Mineralization, focal	11 34
	Necrosis, cortical	4 13
	Necrosis, papillary	7 22

Table 32 (continued)

Organ	Lesion	Number of Lesions 200/100 mg/kg/d Percent (32)*
Liver	Congestion	5 16
	Inflammation, acute focal	1 3
	Necrosis, focal	5 16
Lung	Congestion	7 22
	Atelectasis	1 3
	Inflammation, chronic focal	29 91
	Mineralization, vascular	1 3
Lymph Node		
Cervical	Lymphoid depletion	2 6
Mesenteric	Lymphoid depletion	2 6
Mammary Gland	No lesions observed	
Nerve	Inflammation, chronic focal	1 3
Pancreas	Inflammation, chronic focal	1 3
Parathyroid	No lesions observed	

Table 32 (continued)

Organ	Lesion	Number of Lesions 200/100 mg/kg/d Percent (32)*
Pituitary	No lesions observed	
Prostate	Inflammation, acute	6 19
	Inflammation, chronic	12 38
Salivary Gland	No lesions observed	
Seminal Vesicle	Inflammation, acute	2 6
	Inflammation, chronic	5 16
	Mineralization, focal	1 3
Skeletal Muscle	Inflammation, acute focal	2 6
	Necrosis, focal	2 6
Skin	Inflammation, acute	1 3
Spinal Cord	Vacuolization, gray matter	5 16
Spleen	Congestion	1 3
	Lymphoid depletion	22 69
Stomach	Mineralization, focal	1 3

Table 32 (concluded)

Organ	Lesion	Number of Lesions 200/100 mg/kg/d Percent (32)*
Testes	Abscess	1 3
	Mineralization, focal	4 13
Thymus	Hemorrhage	2 6
	Lymphoid depletion	20 63
Thyroid	Hyperplasia, C-cell	1 3
Trachea	Inflammation, chronic focal	1 3
Urinary Bladder	Hemorrhage	7 22
	Inflammation, acute	7 22
	Inflammation, chronic	3 9

Table 33

SUMMARY OF MICROSCOPIC LESIONS IN HIGH-DOSE (200/100 mg/kg/d) MALE RATS
(Terminal Necropsy, Week 34)

Organ	Lesion	Number of Lesions 200/100 mg/kg/d Percent (34)*
Adrenal		
Cortex	No lesions observed	
	Hemorrhage, periadrenal	1 3
Bone	No lesions observed	
Bone Marrow	Hyperplasia, myeloid	3 9
	Hyperplasia, erythroid	3 9
Brain	Glioma	1 3
	Inflammation, purulent	1 3
Esophagus	No lesions observed	
Heart	Inflammation, chronic focal	6 18
	Mineralization, focal	2 6
	Mineralization, vascular focal	5 15
	Necrosis, focal	2 6
	Fibrosis	2 6

* Number of animals in group.

Table 33 (continued)

Organ	Lesion	Number of Lesions 200/100 mg/kg/d Percent (34)*
Intestines		
Cecum	Edema	1 3
	Necrosis, focal	1 3
	Inflammation, purulent	1 3
Colon	Parasitism	4 12
	Edema	1 3
	Inflammation, acute	1 3
	Mineralization, focal	1 3
	Necrosis, focal	1 3
Duodenum	No lesions observed	
Ileum	Parasitism	1 3
Jejunum	No lesions observed	
Kidney	Nephropathy, chronic focal, mild	9 27
	Inflammation, purulent, parenchyma, focal, mild	1 3
	Atrophy, tubular focal, mild	1 3

Table 33 (continued)

Organ	Lesion	Number of Lesions 200/100 mg/kg/d Percent (34)*
Kidney	Necrosis, papilla, focal, moderate	6 18
	Mineralization, focal	8 24
	Mineralization, vascular, focal	2 6
	Inflammation, chronic focal	4 12
Liver	Necrosis, focal	2 6
	Mineralization, focal, mild	1 3
Lung	Hemorrhage, focal	7 21
	Congestion, diffuse, mild	10 30
	Atelectasis, focal, mild	6 18
	Atelectasis, diffuse	2 6
	Mineralization, interstitial, focal, mild	2 6
	Mineralization, vascular	3 9
	Edema, focal, mild	2 6
	Inflammation, chronic, focal	1 3

Table 33 (continued)

Organ	Lesion	Number of Lesions 200/100 mg/kg/d Percent (34)*
Lung	Pigmented macrophages, focal	1 3
Lymph Node		
Cervical	Hyperplasia, lymphoid	1 3
	Hyperplasia, plasma cell	1 3
Mesenteric	Congestion	1 3
	Mineralization, vascular	2 6
Mammary Gland	Hyperplasia, diffuse, mild	2 6
	Mineralization, vascular	1 3
Pancreas	Lipidosis	1 3
	Inflammation, chronic focal	2 6
Parathyroid	No lesions observed	
Pituitary	No lesions observed	
Prostate	Inflammation, chronic	10 30
	Inflammation, purulent	2 6

Table 33 (continued)

Organ	Lesion	Number of Lesions 200/100 mg/kg/d Percent (34)*
Salivary Gland	Inflammation, chronic focal	1 3
Skin	Necrosis, focal	1 3
	Edema	1 3
	Granulation, tissue	1 3
Skeletal Muscle	Mineralization, focal	1 3
	Necrosis, focal	1 3
	Degeneration, focal mild	1 3
	Regeneration, focal mild	2 6
	Inflammation, acute focal	1 3
Spinal Cord	Hemorrhage, focal	1 3
Spleen	Congestion, moderate	3 9
	Hyperplasia, lymphoid	1 3
	Lymphoid depletion	5 15
	Extramedullary hematopoiesis increased	6 18

Table 33 (continued)

Organ	Lesion	Number of Lesions 200/100 mg/kg/d Percent (34)*
Stomach	Mineralization, focal	2 6
	Mineralization, vascular focal	1 3
	Necrosis, focal	1 3
Testes	Atrophy	1 3
	Mineralization, focal	1 3
	Congestion, focal	1 3
Thymus	Mineralization, vessels, focal mild	1 3
	Hemorrhage, focal	4 12
	Congestion	1 3
	Involution	8 24
Trachea	Inflammation, chronic focal, submucosal	4 12
	Hyperplasia, mucosa, focal	1 3
	Inflammation, chronic lumen, focal mild	1 3

Table 33 (concluded)

Organ	Lesion	Number of Lesions 200/100 mg/kg/d Percent (34)*
Urinary Bladder	Hyperplasia, mucosa	3 9
	Necrosis	4 12
	Inflammation, chronic, submucosa, focal mild	1 3
	Inflammation, chronic	2 6
	Inflammation, acute	2 6
	Inflammation, purulent	1 3
	Hemorrhage	5 15
	Mineralization, focal	1 3

Table 34

SUMMARY OF MICROSCOPIC LESIONS IN HIGH-DOSE (200/100 mg/kg/d) FEMALE RATS
(Terminal Necropsy, Week 34)

Organ	Lesion	Number of Lesions 200/100 mg/kg/d Percent (69)*
Adrenal		
Cortex	Hyperplasia, focal	1 2
	Degeneration, focal	1 2
Medulla	Hyperplasia, focal	2 3
	Inflammation, chronic, mild	1 2
Bone	No lesions observed	
Bone Marrow	Hyperplasia, erythroid	2 3
Brain	Hemorrhage	2 3
	Gliosis, focal	2 3
Esophagus	No lesions observed	
Heart	Inflammation, chronic focal	6 9
Intestines		
Cecum	Edema	2 3
Colon	Parasitism	5 8

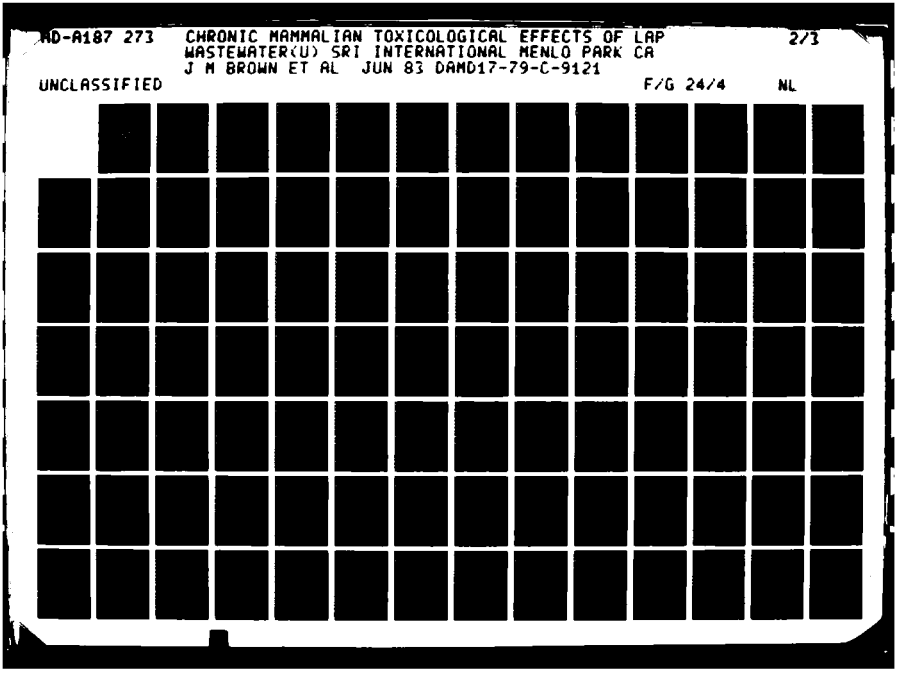
* Number of animals in group.

Table 34 (continued)

Organ	Lesion	Number of Lesions 200/100 mg/kg/d Percent (69)*
Intestine		
Duodenum	Ectopic pancreatic tissue	1 1
Ileum	No lesions observed	
Jejunum	No lesions observed	
Kidney	Hyperplasia, transitional epithelium, focal mild	1 1
	Mineralization, focal	9 13
	Inflammation, chronic focal	10 14
	Degeneration, tubular	1 1
Liver	Necrosis, focal	1 1
	Mineralization, focal mild	1 1
	Inflammation, chronic focal, mild	21 45
	Hyperplasia, bile ductules, focal mild	5 7
	Vacuolization, hepatocytic, focal	2 3
	Foci of cellular alteration	1 1

Table 34 (continued)

Organ	Lesion	Number of Lesions 200/100 mg/kg/d Percent (69)*
Lung	Hemorrhage, focal	14 20
	Hemorrhage, diffuse	1 1
	Congestion, diffuse, mild	4 6
	Atelectasis, focal mild	1 1
	Atelectasis, diffuse	2 3
	Mineralization, vascular	3 4
	Inflammation, chronic focal	6 9
	Pigmented macrophages, focal	4 6
Lymph Node		
Cervical	Hyperplasia, lymphoid	1 1
Mesenteric	Hemorrhage	1 1
Mammary Gland	No lesions observed	
Ovary	Necrosis, focal	1 1
	Hemorrhage	2 3
	Congestion	1 1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WASTEWATER(U) SRI INTERNATIONAL MENLO PARK CA
J M BROWN ET AL JUN 83 DAMD17-79-C-9121
UNCLASSIFIED F/G 24/4 NL

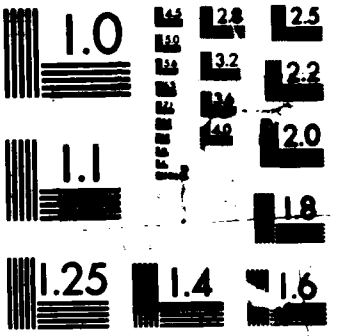

Table 34 (continued)

Organ	Lesion	Number of Lesions 200/100 mg/kg/d Percent (69)*
Pancreas	Lipidosis	2 3
	Inflammation, chronic focal	2 3
	Hyperplasia, ductal, focal	1 1
Parathyroid	No lesions observed	
Pituitary	Inflammation, chronic focal	1 1
	Necrosis, focal	1 1
	Hyperplasia, focal mild	3 4
Salivary Gland	No lesions observed	
Skin	Inflammation, chronic focal	1 1
	Necrosis of fat	3 4
Skeletal Muscle	No lesions observed	
Spinal Cord	Hemorrhage, focal	2 3
Spleen	Congestion, moderate	2 3
	Extramedullary hematopoiesis, increased	2 3
Stomach	No lesions observed	

Table 34 (concluded)

Organ	Lesion	Number of Lesions 200/100 mg/kg/d Percent (69)*
Thymus	No lesions observed	
Trachea	Inflammation, chronic focal, submucosal	19 28
	Hemorrhage, lumen	1 1
Urinary Bladder	Hyperplasia, mucosa	4 6
	Necrosis	1 1
	Inflammation, chronic	6 9
Uterus	Inflammation, purulent	1 1
	Hydrometria	8 12
	Hypertrophy	1 1

Table 35

SUMMARY OF MICROSCOPIC LESIONS IN MALE AND FEMALE RATS
(Dead or Moribund, 1-12 Months)

Organ	Lesion	Number of Lesions		
		Control Percent (1 M)*	12.5 mg/kg/d Percent (1 F)	50 mg/kg/d Percent (7 M)
Adrenal				
Cortex	Degeneration	0 0	1 100	1 14
	Inflammation, chronic focal	0 0	0 0	1 14
Bone	No lesions observed			
Bone Marrow	No lesions observed			
Brain	Infarction	0 0	0 0	1 14
	Inflammation, acute	0 0	0 0	1 14
	Leukemia†	0 0	0 0	1 14
Diaphragm	Inflammation, acute	0 0	1 100	1 14
Eye				
Retina	Inflammation, chronic focal	0 0	0 0	1 14
Heart	Inflammation, chronic focal	0 0	0 0	1 14
	Necrosis, focal	0 0	0 0	3 43

* Number of animals in group.

† All listings of leukemia in this table are Leukemia, Fischer Rat (mononuclear cell).

Table 35 (continued)

Organ	Lesion	Number of Lesions		
		Control Percent (1 M)*	12.5 mg/kg/d Percent (1 F)	50 mg/kg/d Percent (7 M)
Intestine				
Cecum	No lesions observed			
Colon	Parasitism	0 0	0 0	1 14
	Inflammation, chronic	0 0	0 0	1 14
Duodenum	No lesions observed			
Ileum	Parasitism	0 0	1 100	0 0
	Necrosis, lymphoid	0 0	0 0	1 14
Jejunum	No lesions observed			
Kidney	Necrosis, cortical	0 0	1 100	0 0
	Necrosis, papillary	0 0	0 0	1 14
	Inflammation, chronic focal, mild	1 100	1 100	3 43
	Leukemia	0 0	0 0	1 14
	Tubular dilation and atrophy	0 0	1 100	7 100

Table 35 (continued)

Organ	Lesion	Number of Lesions Control Percent (1 M)*	12.5 mg/kg/d Percent (1 F)	50 mg/kg/d Percent (7 M)
Kidney	Inflammation, chronic focal, marked	0 0	0 0	3 43
	Mineralization, focal minor	0 0	1 100	1 14
	Tubular casts	1 100	1 100	7 100
Liver	Hyperplasia, bile ductules	0 0	0 0	1 14
	Dinusoidal dilation	1 100	0 0	0 0
	Leukemia	0 0	0 0	1 14
	Necrosis, focal	0 0	0 0	2 29
	Congestion	0 0	0 0	1 14
Lung	Inflammation, chronic focal	1 100	1 100	6 86
	Congestion	0 0	1 100	3 43
	Edema	1 100	0 0	1 14

Table 35 (continued)

Organ	Lesion	Number of Lesions		
		Control Percent (1 M)*	12.5 mg/kg/d Percent (1 F)	50 mg/kg/d Percent (7 M)
Lung	Hemorrhage	0 0	0 0	1 14
Lymph Node				
Cervical	No lesions observed			
Mesenteric	Edema	0 0	0 0	1 14
Mammary Gland	Leukemia	0 0	0 0	1 14
	Inflammation, chronic focal	0 0	0 0	2 29
Nerve	No lesions observed			
Ovary	Inflammation, purulent	0 0	1 100	0 0
Pancreas	Leukemia	0 0	0 0	1 14
Parathyroid	No lesions observed			
Pituitary	No lesions observed			
Prostate	Inflammation, chronic	0 0	0 0	3 43
	Hyperplasia, focal	0 0	0 0	1 14
	Hemorrhage, focal	0 0	0 0	1 14
Salivary Gland	No lesions observed			

Table 35 (continued)

Organ	Lesion	Number of Lesions		
		Control Percent (1 M)*	12.5 mg/kg/d Percent (1 F)	50 mg/kg/d Percent (7 M)
Seminal Vesicle	Leukemia	0 0	0 0	1 14
Skeletal Muscle	No lesions observed			
Skin	Inflammation, acute	0 0	0 0	1 14
Spinal Cord	Leukemia	0 0	0 0	1 14
Spleen	Leukemia	0 0	0 0	1 14
	Necrosis, focal	0 0	1 100	1 14
	Lymphoid depletion	0 0	0 0	1 14
Stomach	No lesions observed			
Testes	No lesions observed			
Thymus	Lymphoid depletion	1 100	0 0	0 0
	Inflammation, acute	0 0	1 100	0 0
Thyroid	Leukemia	0 0	0 0	1 14
	Cyst	0 0	0 0	1 14
Trachea	No lesions observed			

Table 35 (concluded)

Organ	Lesion	Number of Lesions		
		Control	12.5 mg/kg/d	50 mg/kg/d
		Percent (1 M)*	Percent (1 F)	Percent (7 M)
Urinary Bladder	Inflammation, chronic	0	0	2
		0	0	29
Uterus	Leiomyoma	0	1	0
		0	100	0

Table 36

SUMMARY OF MICROSCOPIC LESIONS IN MALE RATS
(1-Year Necropsy)

Organ	Lesion	Number of Lesions: Control Percent (10)*	12.5 mg/kg/d Percent (10)	50 mg/kg/d Percent (9)
Adrenal				
Cortex	Degeneration, focal	9 90	8 80	9 100
Medulla	Tumor, ganglioneuroma	0 0	1 10	0 0
Bone	No lesions observed			
Bone Marrow	No lesions observed			
Brain	No lesions observed			
Diaphragm	Lipidosis	1 10	0 0	0 0
	Degeneration, focal	0 0	1 10	0 0
Esophagus	No lesions observed			
Heart	Focal necrosis, minor	5 50	6 60	3 33
	Inflammation, chronic	6 60	6 60	2 22
	Inflammation, acute focal	0 0	0 0	1 11
Intestine				
Cecum	No lesions observed			
Colon	Parasitism	1 10	1 10	1 11
Duodenum	No lesions observed			
Ileum	Parasitism	0 0	1 10	0 0

* Number of animals in group.

Table 36 (continued)

Organ	Lesion	Number of Lesions		
		Control Percent (10)*	12.5 mg/kg/d Percent (10)	50 mg/kg/d Percent (9)
Intestine				
Jejunum	No lesions observed			
Kidney	Inflammation, chronic focal	10 100	10 100	9 100
	Tubular regeneration, focal minor	9 90	7 70	5 56
	Hyaline casts, focal, minor	9 90	6 60	5 56
	Infarction	1 10	0 0	0 0
	Mineralization, focal	0 0	0 0	1 11
Liver	Hyperplasia, bile ductules, minimal	5 50	9 90	0 0
	Inflammation, chronic focal	7 70	3 30	3 33
	Necrosis, focal	1 10	4 40	0 0
	Vacuolization, hepatocytic, minimal	5 50	1 10	0 0
Lung	Inflammation, chronic focal, mild	9 90	10 100	9 100
	Inflammation, chronic focal, moderate	1 10	0 0	0 0
	Congestion	0 0	2 20	3 33
	Pigmented macrophages, focal, minimal	0 0	1 10	0 0

Table 36 (continued)

Organ	Lesion	Number of Lesions		
		Control	12.5 mg/kg/d	50 mg/kg/d
		Percent (10)*	Percent (10)	Percent (9)
Lymph Node				
Cervical	Cyst, solitary minor	1	0	0
		10	0	0
Mesenteric	Pigmentation, focal, minimal	0	1	0
		0	10	0
Mammary Gland	Inflammation, chronic focal	0	0	1
		0	0	11
Nerve	No lesions observed			
Pancreas	Inflammation, chronic focal	2	2	0
		20	20	0
	Fibrosis, focal	1	0	0
		10	0	0
Parathyroid	Hyperplasia	0	1	0
		0	10	0
Pituitary	No lesions observed			
Prostate	Hyperplasia, focal	0	1	0
		0	10	0
Testes	Hyperplasia, interstitial cell	4	2	2
		40	20	22
Salivary Gland	Inflammation, chronic focal	0	1	0
		0	10	0
	Lipidosis	0	3	0
		0	30	0
Skeletal Muscle	No lesions observed			
Skin	No lesions observed			

Table 36 (concluded)

Organ	Lesion	Number of Lesions		
		Control Percent (10)*	12.5 mg/kg/d Percent (10)	50 mg/kg/d Percent (9)
Spinal Cord	Hypertrophy, vascular focal	1 10	0 0	0 0
	Hemorrhage, focal	0 0	0 0	1 11
	Vacuolization, white matter, focal	1 10	0 0	0 0
Spleen	Congestion, diffuse moderate	1 10	0 0	1 11
	Lymphocytic depletion, diffuse moderate	0 0	0 0	1 11
Stomach	No lesions observed			
Thymus	Inflammation, acute	1 10	0 0	0 0
	Lymphocytic depletion, diffuse slight	1 10	0 0	0 0
Thyroid	Inflammation, chronic focal	1 10	0 0	0 0
Trachea	Inflammation, chronic focal, minimal/mild	2 20	5 50	2 22
	Ectasia, glands	1 10	0 0	0 0
Urinary Bladder	No lesions observed			

Table 37

SUMMARY OF MICROSCOPIC LESIONS IN FEMALE RATS
(1-Year Sacrifice)

Organ	Lesion	Number of Lesions		
		Control	12.5 mg/kg/d	50 mg/kg/d
		Percent	Percent	Percent
		(10)*	(10)	(10)
Adrenal				
Cortex	Degeneration, focal	0	1	0
		0	10	0
	Inflammation, chronic focal	0	0	2
		0	0	20
Bone	No lesions observed			
Bone Marrow	Focal fibrosis	0	1	0
		0	10	0
Brain	No lesions observed			
Diaphragm	Lipidosis	2	0	0
		20	0	0
Esophagus	No lesions observed			
Heart	Focal necrosis, minor	2	4	3
		20	40	30
	Inflammation, chronic	3	7	2
		30	70	20
Intestine				
Cecum	No lesions observed			
Colon	Parasitism	1	0	0
		10	0	0
Duodenum	No lesions observed			
Ileum	No lesions observed			
Jejunum	No lesions observed			
Kidney	Inflammation, chronic focal	6	7	5
		60	70	50

* Number of animals in group.

Table 37 (continued)

Organ	Lesion	Number of Lesions		
		Control	12.5 mg/kg/d	50 mg/kg/d
		Percent (10)*	Percent (10)	Percent (10)
Kidney	Tubular regeneration, focal, minor	2 20	2 20	1 10
	Hyaline casts, focal, minor	2 20	6 60	0 0
	Mineralization, focal	6 60	8 80	2 20
Liver	Hyperplasia, bile ductules, minimal	3 30	0 0	3 30
	Inflammation, chronic focal	5 50	5 50	7 70
Lung	Inflammation, chronic focal, mild	9 90	10 100	10 100
	Inflammation, chronic focal, moderate	1 10	0 0	0 0
	Hemorrhage, focal	1 10	2 20	0 0
	Congestion	0 0	2 20	0 0
Lymph Node				
Cervical	Pigmentation, focal, minimal	5 50	4 40	0 0
Mesenteric	Pigmentation, focal, minimal	0 0	1 10	0 0
Mammary Gland	Inflammation, acute focal	0 0	1 10	0 0
Nerve	No lesions observed			

Table 37 (continued)

Organ	Lesion	Number of Lesions		
		Control	12.5 mg/kg/d	50 mg/kg/d
		Percent (10)*	Percent (10)	Percent (10)
Ovary	Cyst	1	1	0
		10	10	0
	Inflammation, acute	1	0	0
		10	0	0
Pancreas	Inflammation, chronic focal	0	1	0
		0	10	0
Parathyroid	No lesions observed			
Pituitary	No lesions observed			
Salivary Gland	Inflammation, chronic focal	1	0	0
		10	0	0
Skin	Tumor, keratoacanthoma	0	0	1
		0	0	10
Skeletal Muscle	No lesions observed			
Spinal Cord	No lesions observed			
Spleen	No lesions observed			
Stomach	No lesions observed			
Thymus	No lesions observed			
Thyroid	Hyperplasia, C-cell	1	1	0
		10	10	0
	Necrosis, focal	0	0	1
		0	0	10
Trachea	Inflammation, chronic focal, minimal/mild	0	1	5
		0	10	50
Urinary Bladder	Inflammation, chronic focal	1	0	2
		10	0	20

Table 37 (concluded)

Organ	Lesion	Number of Lesions		
		Control	12.5 mg/kg/d	50 mg/kg/d
		Percent (10)*	Percent (10)	Percent (10)
Uterus	Inflammation, acute	0	1	2
		0	10	20
	Hydrometria	1	0	0
		10	0	0

Table 38

SUMMARY OF MICROSCOPIC LESIONS IN MALE RATS
[Dead or Moribund (13-24 Months) and Terminal Necropsy]

Organ	Lesion	Number of Lesions: Control Percent (64)*	12.5 mg/kg/d Percent (60)	50 mg/kg/d Percent (47)
Adrenal	Hematopoiesis, extramedullary	0	10†	1
		0	17	2
	Leukemia‡	3	2	0
		5	3	0
Cortex	Cyst	0	1	1
		0	2	2
	Degeneration, focal	11	11	8
		17	18	17
	Degeneration, diffuse	0	1	0
		0	2	0
	Hyperplasia, focal	15	26	9
		23	43	19
	Inflammation, chronic	3	0	1
		5	0	2
	Thrombosis, focal	0	1	0
		0	2	0
	Adenoma	2	3	0
		3	5	0
Medulla	Hyperplasia, focal	2	7	3
		3	12	6
	Inflammation, chronic	0	0	1
		0	0	2
	Adenoma	4	7	2
		6	12	4

* Number of animals in group.
† Statistically significant, $p < 0.05$.
‡ All listings of leukemia in this table are Leukemia, Fischer Rat (mononuclear cell).

Table 38 (continued)

Organ	Lesion	Number of Lesions		
		Control	12.5 mg/kg/d	50 mg/kg/d
		Percent (64)*	Percent (60)	Percent (47)
Aorta	Mineralization, focal mild	0	0	4
		0	0	9
Bone (Sternum)	Degeneration, focal	4	2	1
		6	3	2
Bone Marrow	Congestion	1	0	0
		2	0	0
	Cyst	0	1	0
		0	2	0
	Hypercellularity, NOS	1	2	0
		2	3	0
	Hyperplasia, granulocytic	3	2	1
		5	3	2
	Hyperplasia, myeloid	5	1	4
		8	2	9
	Pigmentation, focal	1	0	0
		2	0	0
	Leukemia	10	5	3
		16	8	6
Brain	Congestion	1	0	1
		2	0	2
	Cyst, focal	0	0	1
		0	0	2
	Hemorrhage, focal	2	7	0
		3	12	0
	Inflammation, chronic focal	1	1	0
		2	2	0
	Inflammation, purulent focal	1	0	0
		2	0	0

Table 38 (continued)

Organ	Lesion	Number of Lesions		
		Control	12.5 mg/kg/d	50 mg/kg/d
		Percent	Percent	Percent
		(64)*	(60)	(47)
Brain	Mineralization, focal	1	1	0
		2	2	0
	Necrosis, focal	1	0	0
		2	0	0
	Carcinoma, metastatic	2	1	0
		3	2	0
	Granular cell tumor	0	0	1
		0	0	2
	Leukemia	1	1	0
		2	2	0
Diaphragm	Hemorrhage, focal	0	0	1
		0	0	2
	Inflammation, chronic	3	0	3
		5	0	6
	Mineralization, focal	0	0	1
		0	0	2
	Pigmentation, focal	0	0	1
		0	0	2
	Leukemia	1	0	0
		2	0	0
Esophagus	Inflammation, acute focal	1	1	2
		2	2	4
	Inflammation, chronic focal	0	1	1
		0	2	2
Heart	Cardiomyopathy, mild	41	46	24
		64	77	51

Table 38 (continued)

Organ	Lesion	Number of Lesions		
		Control	12.5 mg/kg/d	50 mg/kg/d
		Percent (64)*	Percent (60)	Percent (47)
Heart	Cardiomyopathy, moderate/marked	10 16	11 18	7 15
	Hemorrhage, focal	0 0	2 3	0 0
	Inflammation, chronic focal	1 2	3 5	1 2
	Mineralization, focal mild	1 2	0 0	20† 43
	Necrosis, focal	1 2	2 3	2 4
	Thrombosis, atrial	1 2	1 2	0 0
	Leukemia	4 6	2 3	0 0
	Neurilemoma	0 0	0 0	1 2
	Sarcoma, metastatic	1 2	0 0	0 0
Intestine				
Cecum	Hemorrhage, focal	0 0	1 2	0 0
	Inflammation, purulent	1 2	0 0	0 0
	Inflammation, chronic	0 0	1 2	1 2

Table 38 (continued)

Organ	Lesion	Number of Lesions		
		Control	12.5 mg/kg/d	50 mg/kg/d
		Percent (64)*	Percent (60)	Percent (47)
Intestine				
Cecum	Mineralization, focal	0	0	1
		0	0	2
	Parasitism	1	0	0
		2	0	0
Colon	Edema	1	0	0
		2	0	0
	Mineralization, focal	0	0	4
		0	0	9
	Parasitism	10	10	4
		16	17	9
	Pigmentation, focal	0	0	1
		0	0	2
	Fibrosarcoma, metastatic	1	0	0
		2	0	0
	Neurilemoma	0	1	0
		0	2	0
Duodenum	Mineralization, focal	0	0	1
		0	0	2
	Pigmentation, focal	0	0	1
		0	0	2
	Leiomyosarcoma	1	0	0
		2	0	0

Table 38 (continued)

Organ	Lesion	Number of Lesions		
		Control	12.5 mg/kg/d	50 mg/kg/d
		Percent	Percent	Percent
		(64)*	(60)	(47)
Intestine				
Ileum	Cyst	0	2	0
		0	3	0
	Hyperplasia, lymphoid	1	0	0
		2	0	0
	Inflammation, chronic	0	1	1
		0	2	2
	Necrosis, lymphoid	1	0	0
		2	0	0
	Parasitism	2	0	0
		3	0	0
	Pigmentation, focal	0	0	1
		0	0	2
	Leukemia	1	0	0
		2	0	0
Jejunum	Parasitism	1	0	0
		2	0	0
	Pigmentation, focal	0	0	1
		0	0	2
Kidney	Congestion	3	0	0
		5	0	0
	Cyst	0	1	2
		0	2	4
	Hemorrhage, focal	2	1	0
		3	2	0

Table 38 (continued)

Organ	Lesion	Number of Lesions		
		Control	12.5 mg/kg/d	50 mg/kg/d
		Percent (64)*	Percent (60)	Percent (47)
Kidney	Hydronephrosis	0	0	8†
		0	0	17
	Hyperplasia, transitional epithelium, mild	3	19†	8
		5	32	17
	Hyperplasia, transitional epithelium, moderate	0	3	4
		0	5	9
	Inflammation, acute papillary	0	0	1
		0	0	2
	Inflammation, chronic	2	1	7
		3	2	15
	Inflammation, purulent focal	1	0	0
		2	0	0
	Infarction, focal	3	2	0
		5	3	0
	Mineralization, focal	0	0	18†
		0	0	38
	Necrosis, cortical	2	0	1
		3	0	2
	Necrosis, papillary	0	0	15†
		0	0	32
	Nephropathy, mild	19	14	18
		30	23	38
	Nephropathy, moderate	40	44	24
		63	73	51
	Nephropathy, marked	1	0	5
		2	0	11

Table 38 (continued)

Organ	Lesion	Number of Lesions		
		Control	12.5 mg/kg/d	50 mg/kg/d
		Percent (64)*	Percent (60)	Percent (47)
Kidney	Pigmentation, focal	0	1	0
		0	2	0
	Leukemia	4	1	1
		6	2	2
Liver	Congestion	0	0	9†
		0	0	19
	Cyst, focal	5	0	1
		8	0	2
	Fibrosis, focal	2	0	1
		3	0	2
	Foci of cellular alteration	24	34	5†
		38	57	11
	Hyperplasia, hepatocytic, focal	0	5	2
		0	8	4
	Hyperplasia, bile ductules	61	59	40
		95	98	85
	Hematopoiesis, extramedullary	1	0	0
		2	0	0
	Hepatocyte, atypia, diffuse	0	1	0
		0	2	0
	Inflammation, chronic focal	6	8	3
		9	13	6
	Necrosis, focal	6	8	0
		9	13	0
	Necrosis, diffuse	0	0	1
		0	0	2

Table 38 (continued)

Organ	Lesion	Number of Lesions		
		Control	12.5 mg/kg/d	50 mg/kg/d
		Percent (64)*	Percent (60)	Percent (47)
Liver	Sinusoidal dilation, focal	0	5	0
		0	8	0
	Pigmentation, focal	1	0	0
		2	0	0
	Degeneration, hepatocytic, mild	0	1	1
		0	2	2
	Vacuolization, hepatocytic, mild	16	25	4
		25	42	9
	Vacuolization, hepatocytic, moderate	2	1	1
		3	2	2
	Hepatocellular carcinoma	0	0	1
		0	0	2
	Sarcoma, metastatic	2	0	0
		3	0	0
	Leukemia	9	2	3
		14	3	6
Lung	Alveolar histiocytosis, focal	6	7	8
		9	12	17
	Atelectasis, focal	1	1	2
		2	2	4
	Congestion	13	12	21†
		20	20	45
	Edema	3	0	5
		5	0	11
	Emphysema, focal	0	0	1
		0	0	2
	Foreign material, focal	1	0	1
		2	0	2

Table 38 (continued)

Organ	Lesion	Number of Lesions		
		Control	12.5 mg/kg/d	50 mg/kg/d
		Percent	Percent	Percent
		(64)*	(60)	(47)
Lung	Hemorrhage	5	8	6
		8	13	13
	Hyperplasia, bronchial epithelium, focal	0	1	0
		0	2	0
	Inflammation, chronic focal	19	24	8
		30	40	17
	Inflammation, interstitial	2	3	2
		3	5	4
	Mineralization, focal vascular	12	21	12
		19	35	26
	Mineralization, interstitial	0	0	11†
		0	0	23
	Pigmented macrophages, focal, minimal/mild	8	21†	7
		13	35	15
	Pulmonary adenomatosis	0	2	0
		0	3	0
	Adenoma	0	1	0
		0	2	0
	Carcinoma	0	2	1
		0	3	2
	Adenocarcinoma, metastatic	1	1	0
		2	2	0
	Leukemia	7	4	1
		11	7	2

Table 38 (continued)

Organ	Lesion	Number of Lesions		
		Control	12.5 mg/kg/d	50 mg/kg/d
		Percent (64)*	Percent (60)	Percent (47)
Lymph Nodes				
Brachial	Leukemia	1	0	0
		2	0	0
Cervical	Cyst, focal	3	9	0
		5	15	0
	Edema	0	2	0
		0	3	0
	Fibrosis	0	1	0
		0	2	0
	Hyperplasia, lymphoid	1	4	2
		2	7	4
	Hyperplasia, plasma cell	1	2	1
		2	3	2
	Inflammation, chronic	1	0	0
		2	0	0
	Leukemia	0	0	2
		0	0	4
Hepatic	Leukemia	2	0	0
		3	0	0
Mesenteric	Congestion	0	0	2
		0	0	4
	Cyst, focal	0	2	0
		0	3	0
	Edema	0	2	2
		0	3	4

Table 38 (continued)

Organ	Lesion	Number of Lesions		
		Control Percent (64)*	12.5 mg/kg/d Percent (60)	50 mg/kg/d Percent (47)
Lymph Nodes				
Mesenteric	Hemorrhage	1 2	1 2	0 0
	Hyperplasia, lymphoid	1 2	5 8	1 2
	Inflammation, chronic	0 0	1 2	0 0
	Necrosis, focal	0 0	1 2	0 0
	Necrosis, adjacent fat	1 2	0 0	0 0
	Mesothelioma, external surface	0 0	0 0	1 2
	Leukemia	5 8	1 2	1 2
Pancreatic	Leukemia	1 2	0 0	0 0
Thymic	Edema	0 0	1 2	0 0
	Hemorrhage	1 2	3 5	1 2
	Hemosiderosis, mild	0 0	2 3	0 0
	Hyperplasia, lymphoid	0 0	1 2	0 0
	Hyperplasia, plasma cell	0 0	2 3	0 0

Table 38 (continued)

Organ	Lesion	Number of Lesions		
		Control	12.5 mg/kg/d	50 mg/kg/d
		Percent (64)*	Percent (60)	Percent (47)
Lymph Node				
Thymic	Inflammation, chronic focal	0 0	1 2	0 0
	Adenocarcinoma, metastatic	1 2	0 0	0 0
Mammary Gland	Cyst	1 2	4 7	0 0
	Ectasia, ductular, mild/ moderate	10 16	14 23	2 4
	Ectasia, ductular, marked (Galactocele)	1 2	0 0	2 4
	Fibrosis, focal moderate	1 2	1 2	0 0
	Hyperplasia, mild	0 0	1 2	1 2
	Inflammation, chronic	1 2	0 0	0 0
	Pigmentation	0 0	2 3	0 0
	Thrombosis, focal	0 0	0 0	1 2
	Adenoma	1 2	0 0	0 0
	Adenocarcinoma	0 0	1 2	0 0

Table 38 (continued)

Organ	Lesion	Number of Lesions		
		Control	12.5 mg/kg/d	50 mg/kg/d
		Percent (64)*	Percent (60)	Percent (47)
Mammary Gland	Fibroadenoma	2 3	0 0	0 0
	Leukemia	0 0	0 0	1 2
Masses				
Abdominal Cavity	Lipoma	1 2	0 0	0 0
	Mesothelioma	0 0	0 0	1 2
	Necrosis of fat	2 3	1 2	2 4
	Neurilemoma	1 2	0 0	0 0
Foot	Osteoma	0 0	0 0	1 2
Preputial Gland	Adenoma	0 0	2 3	0 0
	Adenocarcinoma	1 2	3 5	2 4
Subcutaneous	Fibroma	2 3	2 3	2 4
	Hemangiopericytoma	1 2	0 0	0 0
	Hemangiosarcoma	0 0	1 2	0 0
	Myxoma	1 2	0 0	0 0

Table 38 (continued)

Organ	Lesion	Number of Lesions		
		Control Percent (64)*	12.5 mg/kg/d Percent (60)	50 mg/kg/d Percent (47)
Masses				
Subcutaneous	Necrosis of fat	1 2	0 0	0 0
	Sarcoma	1 2	0 0	0 0
Zymbal's Gland	Carcinoma	0 0	0 0	1 2
Muscle	Degeneration, focal	0 0	0 0	1 2
	Edema, focal	1 2	0 0	0 0
	Inflammation, chronic	0 0	1 2	1 2
	Mineralization, focal	0 0	0 0	2 4
	Leukemia	1 2	1 2	0 0
Pancreas	Atrophy, focal	24 38	22 37	5† 11
	Atrophy, diffuse	1 2	1 2	0 0
	Cyst, focal	0 0	2 3	0 0
	Degeneration, focal	0 0	1 2	0 0
	Hyperplasia, acinar cell, focal	1 2	4 7	0 0

Table 38 (continued)

Organ	Lesion	Number of Lesions		
		Control	12.5 mg/kg/d	50 mg/kg/d
		Percent (64)*	Percent (60)	Percent (47)
Pancreas	Hyperplasia, ductular, focal	2 3	2 3	0 0
	Hyperplasia, islet cell	15 23	10 17	1† 2
	Fibrosis, focal	0 0	0 0	1 2
	Inflammation, chronic focal	19 30	28 47	9 19
	Lipidosis	24 38	31 52	8 17
	Mineralization, focal	0 0	1 2	5† 11
	Vacuolization	3 5	0 0	5 11
	Necrosis of fat, adjacent	0 0	0 0	1 2
	Adenoma, islet cell	2 3	2 3	0 0
	Adenocarcinoma	1 2	0 0	0 0
	Fibrosarcoma, metastatic	1 2	0 0	0 0
	Mesothelioma, surface	0 0	0 0	1 2
	Leukemia	3 5	0 0	1 2

Table 38 (continued)

Organ	Lesion	Number of Lesions		
		Control Percent (64)*	12.5 mg/kg/d Percent (60)	50 mg/kg/d Percent (47)
Parathyroid	Hyperplasia	3 5	2 3	9† 19
Pituitary				
Anterior	Congestion	7 11	0† 0	4 9
	Cyst	0 0	2 3	1 2
	Hyperplasia	22 34	27 45	12 26
	Vacuolization	0 0	0 0	1 2
	Adenoma	16 25	18 30	3† 6
	Carcinoma	3 5	5 8	1 2
	Leukemia	1 2	0 0	0 0
Posterior	Gliosis	0 0	2 3	2 4
Prostate	Congestion	0 0	0 0	1 2
	Hyperplasia, focal, minimal/ mild	30 47	29 48	7† 15
	Hyperplasia, focal, moderate	0 0	1 2	1 2

Table 38 (continued)

Organ	Lesion	Number of Lesions		
		Control	12.5 mg/kg/d	50 mg/kg/d
		Percent (64)*	Percent (60)	Percent (47)
Prostate	Inflammation, chronic focal	23 36	20 33	13 28
	Inflammation, diffuse	0 0	2 3	15† 32
	Inflammation, purulent	0 0	0 0	1 2
	Edema	0 0	1 2	0 0
	Mesothelioma, surface	0 0	0 0	1 2
	Leukemia	0 0	0 0	1 2
Salivary Gland	Atrophy	0 0	2 3	0 0
	Congestion	1 2	0 0	0 0
	Ectasia, ductular	0 0	0 0	1 2
	Hemorrhage, focal	0 0	2 3	0 0
	Hyperplasia, focal mild	3 5	5 8	2 4
	Hyperplasia, ductular, focal	2 2	3 5	0 0
	Hyperplasia, ductular mucosa, focal	0 0	5 8	1 2

Table 38 (continued)

Organ	Lesion	Number of Lesions		
		Control	12.5 mg/kg/d	50 mg/kg/d
		Percent	Percent	Percent
		(64)*	(60)	(47)
Salivary Gland	Inflammation, chronic focal	3	4	2
		5	7	4
	Lipidosis, mild	39	39	6†
		61	65	13
	Vacuolization, acinar	0	1	2
		0	2	4
	Carcinoma	0	1	0
		0	2	0
	Fibrosarcoma	0	1	0
		0	2	0
	Sarcoma	0	1	0
		0	2	0
Skin	Keratoacanthoma	1	0	1
		2	0	2
	Squamous cell carcinoma	1	1	0
		2	2	0
	Inflammation, chronic focal	0	0	2
		0	0	4
	Inclusion cyst, epidermal	0	0	1
		0	0	2
Scrotal Sac	Inflammation, chronic diffuse	0	0	1
		0	0	2
	Necrosis	0	0	1
		0	0	2
Seminal Vesicle	Atrophy	18	28	4†
		28	47	9
	Cyst	0	1	0
		0	2	0

Table 38 (continued)

Organ	Lesion	Number of Lesions		
		Control	12.5 mg/kg/d	50 mg/kg/d
		Percent (64)*	Percent (60)	Percent (47)
Seminal Vesicle	Edema	0	0	1
		0	0	2
	Inflammation, chronic	0	0	11†
		0	0	23
	Mesothelioma, surface	0	0	1
		0	0	2
Spinal Cord	Gliosis, focal	0	1	1
		0	2	2
	Hemorrhage, focal	8	2	0
		13	3	0
	Inflammation, purulent	1	0	0
		2	0	0
	Mineralization, dura, focal	0	1	0
		0	2	0
	Vacuolization, gray matter, mild focal	35	44	10†
		55	73	21
	Vacuolization, white matter, mild focal	43	47	6†
		67	78	13
	Leukemia	1	0	0
		2	0	0
Spleen	Congestion	5	2	2
		8	3	4
	Hematopoiesis, extramedullary, moderate	2	2	0
		3	3	0
	Lymphoid depletion, mild	0	0	8†
		0	0	17
	Necrosis, focal	1	2	0
		2	3	0

Table 38 (continued)

Organ	Lesion	Number of Lesions		
		Control	12.5 mg/kg/d	50 mg/kg/d
		Percent (64)*	Percent (60)	Percent (47)
Spleen	Fibrosarcoma	1 2	0 0	0 0
	Leukemia	12 19	9 15	4 9
	Infarction	0 0	0 0	1 2
Stomach				
Forestomach	Hyperplasia, epithelial, mild	0 0	6† 10	1 2
	Ulceration	0 0	1 2	0 0
	Papilloma	0 0	0 0	1 2
	Squamous cell carcinoma	1 2	0 0	0 0
Glandular Stomach	Adhesion	0 0	1 2	0 0
	Edema, focal	0 0	4 7	6 13
	Fibrosis	1 2	0 0	0 0
	Glandular dilation and atrophy	14 22	32† 54	11 23
	Inflammation, chronic focal	5 8	0 0	2 4
	Mineralization, mild	0 0	0 0	20† 43

Table 38 (continued)

Organ	Lesion	Number of Lesions		
		Control	12.5 mg/kg/d	50 mg/kg/d
		Percent (64)*	Percent (60)	Percent (47)
Stomach				
Glandular Stomach	Mineralization, moderate	0	0	2
		0	0	4
	Leukemia	4	0	0
		6	0	0
	Sarcoma	1	0	0
		2	0	0
	Fibrosarcoma, metastatic	1	0	0
		2	0	0
Tail	Inflammation, chronic	0	0	1
		0	0	2
	Necrosis	0	0	1
		0	0	2
	Fibrosarcoma	0	1	0
		0	2	0
Testes	Atrophy	48	52	28
		75	87	60
	Hyperplasia, interstitial cell	4	2	6
		6	3	13
	Hemorrhage	1	1	0
		2	2	0
	Inflammation, chronic	0	5	3
		0	8	6
	Mineralization, focal	0	6†	4
		0	10	9
	Necrosis, focal	0	0	1
		0	0	2

Table 38 (continued)

Organ	Lesion	Number of Lesions		
		Control	12.5 mg/kg/d	50 mg/kg/d
		Percent (64)*	Percent (60)	Percent (47)
Testes	Necrosis of adjacent fat	0 0	1 2	0 0
	Mesothelioma, serosa	0 0	3 5	1 2
	Interstitial cell tumor	53 83	56 93	25† 53
Thymus	Congestion	0 0	0 0	3 6
	Cyst	0 0	2 3	0 0
	Lymphoid depletion	0 0	0 0	1 2
	Hyperplasia, epithelial cell	0 0	0 0	1 2
	Inflammation, chronic focal, mild	0 0	1 2	0 0
	Involution	47 73	48 80	31 66
	Mineralization, focal	0 0	0 0	1 2
	Leukemia	4 6	2 3	2 4
Thyroid	Cyst, focal	3 5	10 17	2 4
	Degeneration, focal	0 0	1 2	0 0
	Hemorrhage, focal	0 0	1 2	0 0

Table 38 (continued)

Organ	Lesion	Number of Lesions		
		Control	12.5 mg/kg/d	50 mg/kg/d
		Percent (64)*	Percent (60)	Percent (47)
Thyroid	Hyperplasia, follicular cell, focal	1 2	1 2	0 0
	Hyperplasia, C-cell	10 16	13 22	1 2
	Adenoma, C-cell	2 3	1 2	0 0
	Carcinoma, C-cell	5 8	9 15	2 4
	Adenocarcinoma	1 2	3 5	1 2
	Inflammation, chronic focal	2 3	1 2	0 0
Trachea	Degeneration, mucosa	1 2	0 0	0 0
	Ectasia, submucosal glands	21 33	23 38	6† 13
	Foreign body, lumen	0 0	0 0	1 2
	Hyperplasia, mucosa, focal	0 0	2 3	1 2
	Inflammation, chronic focal	6 9	9 15	11 23
Urinary Bladder	Hemorrhage	1 2	2 3	11† 23
	Hyperplasia, mucosa	2 3	2 3	9† 19
	Fibroplasia, serosa	0 0	0 0	10† 21

Table 38 (concluded)

Organ	Lesion	Number of Lesions		
		Control	12.5 mg/kg/d	50 mg/kg/d
		Percent (64)*	Percent (60)	Percent (47)
Urinary Bladder	Inflammation, chronic	2 3	8 13	15† 32
	Inflammation, acute	0 0	0 0	2 4
	Mineralization	0 0	0 0	2 4
	Necrosis	0 0	0 0	11† 23
	Papilloma	0 0	1 2	1 2
	Mesothelioma, serosa	0 0	0 0	1 2
	Leukemia	0 0	1 2	0 0

Table 39

SUMMARY OF MICROSCOPIC LESIONS IN FEMALE RATS
[Dead or Moribund (13-24 Months) and Terminal Necropsy]

Organ	Lesion	Number of Lesions		
		Control	12.5 mg/kg/d	50 mg/kg/d
		Percent (64)*	Percent (59)	Percent (60)
Adrenal	Hematopoiesis (extramedullary)	2 3	0 0	2 3
	Leukemia‡	4 6	3 5	1 2
	Congestion	0 0	0 0	1 2
Cortex	Atrophy	1 2	0 0	0 0
	Cyst	8 13	6 10	1 2
	Degeneration, focal	28 44	23 39	20 33
	Hyperplasia, focal	25 39	19 32	13 22
	Inflammation, chronic focal	2 3	0 0	2 3
	Adenoma	0 0	2 3	1 2
	Carcinoma	0 0	1 2	0 0
Medulla	Cyst	1 2	0 0	0 0
	Hyperplasia, focal	1 2	2 3	2 3

* Number of animals in group.

‡ All listings of leukemia in this table are Leukemia, Fischer Rat (mononuclear cell).

Table 39 (continued)

Organ	Lesion	Number of Lesions		
		Control	12.5 mg/kg/d	50 mg/kg/d
		Percent (64)*	Percent (59)	Percent (60)
Adrenal				
Medulla	Inflammation, chronic focal	0	1	0
		0	2	0
	Adenoma	0	2	2
		0	3	3
	Carcinoma	1	0	0
		2	0	0
Bone (Sternum)	Degeneration, focal mild	9	8	3
		14	14	5
Bone Marrow	Atrophy	1	1	1
		2	2	2
	Fibrosis, focal	0	1	1
		0	2	2
	Hyperplasia, granulocytic	0	1	7†
		0	2	12
	Hyperplasia, myeloid	2	2	3
		3	3	5
	Leukemia	5	9	6
		8	15	10
Brain	Cyst, focal	1	0	0
		2	0	0
	Fibrosis (dura), focal	0	0	1
		0	0	2
	Gliosis, focal	2	1	0
		3	2	0

† Statistically significant, $p < 0.05$.

Table 39 (continued)

Organ	Lesion	Number of Lesions		
		Control	12.5 mg/kg/d	50 mg/kg/d
		Percent (64)*	Percent (59)	Percent (60)
Brain	Hemorrhage, focal	0	0	4
		0	0	7
	Hydrocephalus	1	0	0
		2	0	0
	Inflammation, chronic focal	1	1	0
		2	2	0
	Mineralization, focal	3	0	1
		5	0	2
	Astrocytoma	0	0	1
		0	0	2
	Ependymoma	0	1	0
		0	2	0
	Glioma	1	0	0
		2	0	0
	Carcinoma, metastatic	2	1	0
		3	2	0
	Leukemia	0	1	1
		0	2	2
Diaphragm	Inflammation, chronic focal	2	7	3
		3	12	5
	Atrophy	0	0	1
		0	0	2
	Fibrosarcoma, metastatic	0	0	1
		0	0	2
Esophagus	Hyperplasia, epithelial	0	0	1
		0	0	2
	Inflammation, chronic focal	0	0	1
		0	0	2

Table 39 (continued)

Organ	Lesion	Number of Lesions		
		Control	12.5 mg/kg/d	50 mg/kg/d
		Percent (64)*	Percent (59)	Percent (60)
Esophagus	Mineralization, focal	1	0	0
		2	0	0
Heart	Cardiomyopathy, mild	45	45	39
		70	76	65
	Cardiomyopathy, moderate/ marked	8	2	5
		13	3	8
	Inflammation, chronic focal	6	4	1
		9	7	2
	Mineralization, focal	0	2	0
		0	3	0
	Necrosis, focal	1	0	0
		2	0	0
	Leukemia	2	3	1
		3	5	2
	Adenocarcinoma, metastatic	0	0	1
		0	0	2
	Neurilemoma	0	2	0
		0	3	0
Intestine				
Cecum	Edema	0	0	1
		0	0	2
	Inflammation, chronic	0	0	1
		0	0	2
	Parasitism	1	0	0
		2	0	0
	Leukemia	1	0	0
		2	0	0

Table 39 (continued)

Organ	Lesion	Number of Lesions		
		Control	12.5 mg/kg/d	50 mg/kg/d
		Percent (64)*	Percent (59)	Percent (60)
Intestine				
Colon	Congestion	0	0	1
		0	0	2
	Inflammation, focal	0	1	0
		0	2	0
	Mineralization, focal	0	0	1
		0	0	2
	Parasitism	7	6	6
		11	10	10
	Fibrosarcoma, metastatic	0	0	1
		0	0	2
	Leukemia	1	0	0
		2	0	0
Duodenum	No lesions observed			
Ileum	Atrophy, mild	0	0	1
		0	0	2
	Mineralization, focal	0	0	2
		0	0	3
	Parasitism	1	1	0
		2	2	0
	Adenocarcinoma	0	0	1
		0	0	2
	Fibrosarcoma, metastatic	0	0	1
		0	0	2
Jejunum	No lesions observed			

Table 39 (continued)

Organ	Lesion	Number of Lesions		
		Control	12.5 mg/kg/d	50 mg/kg/d
		Percent	Percent	Percent
		(64)*	(59)	(60)
Kidney	Cyst	2	1	0
		3	2	0
	Hydronephrosis	0	0	2
		0	0	3
	Hyperplasia, transitional epithelium, mild	11	7	12
		17	12	20
	Infarction, focal	1	2	2
		2	3	3
	Inflammation, chronic focal	1	0	0
		2	0	0
	Inflammation, purulent	0	1	0
		0	2	0
	Necrosis, cortical	2	0	0
		3	0	0
	Necrosis, papillary	0	0	1
		0	0	2
	Nephropathy, mild	55	50	51
		86	85	85
	Nephropathy, moderate	4	4	2
		6	7	3
	Mineralization, mild	8	6	2
		13	10	3
	Pigmentation, focal	1	0	0
		2	0	0
	Adenoma	0	0	1
		0	0	2

Table 39 (continued)

Organ	Lesion	Number of Lesions		
		Control	12.5 mg/kg/d	50 mg/kg/d
		Percent (64)*	Percent (59)	Percent (60)
Kidney	Adenocarcinoma	0	0	1
		0	0	2
	Leukemia	4	1	2
		6	2	3
Liver	Congestion	0	1	2
		0	2	3
	Cyst, focal	1	0	3
		2	0	5
	Degeneration, hepatocyte	0	2	0
		0	3	0
	Foci of cellular alteration	45	32	30
		70	54	50
	Hematopoiesis (extramedullary)	0	1	1
		0	2	2
	Hyperplasia, hepatocyte focal	4	5	3
		6	9	5
	Hyperplasia, bile ductules	30	22	27
		47	37	57
	Hemorrhage, focal	1	2	0
		2	3	0
	Inflammation, chronic focal	33	37	41
		52	63	68
	Inflammation, chronic diffuse	0	1	0
		0	2	0
	Necrosis	2	4	6
		3	7	10
	Pigmentation, focal	0	1	1
		0	2	2

Table 39 (continued)

Organ	Lesion	Number of Lesions		
		Control	12.5 mg/kg/d	50 mg/kg/d
		Percent	Percent	Percent
		(64)*	(59)	(60)
Liver	Sinusoidal dilation, focal	0	1	1
		0	2	2
	Vacuolization, hepatocytic, focal	8	3	0†
		13	5	0
	Vacuolization, hepatocytic, diffuse	4	2	1
		7	3	2
	Adenocarcinoma, metastatic	1	0	1
		2	0	2
	Leukemia	7	7	3
		11	12	5
Lung	Atelectasis	0	0	1
		0	0	2
	Congestion	3	3	4
		5	5	7
	Edema	1	1	2
		2	2	3
	Hemorrhage	7	4	5
		11	7	8
	Histiocytosis, alveolar	3	4	3
		5	7	5
	Hyperplasia, bronchial epithelium	0	2	0
		0	3	0
	Inflammation, chronic focal	27	25	28
		42	42	47
	Inflammation, interstitial	1	4	6
		2	7	10

Table 39 (continued)

Organ	Lesion	Number of Lesions		
		Control	12.5 mg/kg/d	50 mg/kg/d
		Percent	Percent	Percent
		(64)*	(59)	(60)
Lung	Inflammation, acute	1	0	0
		2	0	0
	Infarction, focal	0	0	1
		0	0	2
	Mineralization, focal vascular	31	25	32
		48	42	53
	Mineralization, interstitial	0	3	0
		0	5	0
	Pigmented macrophages, focal	45	32	29†
		70	54	48
	Pulmonary adenomatosis	4	1	2
		6	2	3
	Adenocarcinoma, metastatic	0	0	1
		0	0	2
	Carcinoma, metastatic	1	1	0
		2	2	0
	Carcinoma, bronchioalveolar	0	0	1
		0	0	2
	Leukemia	4	6	2
		6	10	3
	Sarcoma, metastatic	0	1	0
		0	2	0
Lymph Node				
Cervical	Cyst	1	1	0
		2	2	0
	Congestion	0	3	0
		0	5	0

Table 39 (continued)

Organ	Lesion	Number of Lesions		
		Control	12.5 mg/kg/d	50 mg/kg/d
		Percent (64)*	Percent (59)	Percent (60)
Lymph Node				
Cervical	Hemorrhage	0	0	1
		0	0	2
	Hyperplasia, lymphoid	1	1	1
		2	2	2
	Hyperplasia, plasma cell	2	2	0
		3	3	0
	Pigmentation, focal	1	0	0
		2	0	0
	Leukemia	1	3	1
		2	5	2
Brachial	Leukemia	0	1	0
		0	2	0
Inguinal	Leukemia	0	1	0
		0	2	0
Hepatic	Leukemia	1	0	0
		2	0	0
Mammary	Leukemia	0	1	0
		0	2	0
Mesenteric	Congestion	0	0	1
		0	0	2
	Edema	0	1	0
		0	2	0
	Hemorrhage	1	0	0
		2	0	0
	Hyperplasia, lymphoid	5	0	1
		8	0	2

Table 39 (continued)

Organ	Lesion	Number of Lesions		
		Control	12.5 mg/kg/d	50 mg/kg/d
		Percent	Percent	Percent
		(64)*	(59)	(60)
Lymph Node				
Mesenteric	Inflammation, chronic	0	1	5
		0	2	8
	Pigmentation, focal	0	2	3
		0	3	5
	Leukemia	3	5	1
		5	9	2
	Adenocarcinoma, metastatic	0	0	1
		0	0	2
	Sarcoma, metastatic	0	0	1
		0	0	2
Pancreatic	Cyst	1	0	0
		2	0	0
	Pigmentation, focal	1	1	0
		2	2	0
	Leukemia	0	0	1
		0	0	2
Thymic	Congestion	0	1	1
		0	2	2
	Hemorrhage	1	0	0
		2	0	0
	Hyperplasia, lymphoid	1	0	0
		2	0	0
	Pigmentation, focal	1	2	5
		2	3	8

Table 39 (continued)

Organ	Lesion	Number of Lesions		
		Control	12.5 mg/kg/d	50 mg/kg/d
		Percent (64)*	Percent (59)	Percent (60)
Lymph Node				
Thymic	Leukemia	1	0	0
		2	0	0
Mammary Gland	Cyst	2	0	0
		3	0	0
	Ectasia, ductular, mild/ moderate	43	36	25†
		67	61	42
	Ectasia, ductular, marked (Galactocele)	23	6†	3†
		36	10	5
	Hyperplasia, mild	0	2	0
		0	3	0
	Inflammation, chronic	0	1	0
		0	2	0
	Adenoma	3	0	0
		5	0	0
	Adenocarcinoma	1	0	2
		2	0	3
	Fibroma	1	0	0
		2	0	0
	Fibroadenoma	20	6†	2†
		31	10	3
	Sarcoma	0	0	1
		0	0	2

Table 39 (continued)

Organ	Lesion	Number of Lesions Control Percent (64)*	12.5 mg/kg/d Percent (59)	50 mg/kg/d Percent (60)
Masses				
Abdominal Fat	Necrosis of fat	1 2	3 5	4 7
	Lipoma	0 0	1 2	0 0
Clitoral Gland	Adenoma	1 2	0 0	2 3
	Adenocarcinoma	0 0	1 2	0 0
Ear (Pinna)	Neurilemoma	0 0	1 2	0 0
Foot	Hemangiosarcoma	1 2	0 0	0 0
Jaw	Squamous cell carcinoma	1 2	1 2	0 0
Subcutaneous	Adenocarcinoma	0 0	0 0	1 2
	Fibroma	1 2	1 2	1 2
	Sarcoma	2 3	0 0	0 0
Pelvis	Carcinoma, metastatic	0 0	0 0	1 2
Vaginal	Sarcoma, metastatic	0 0	1 2	1 2
Zymbal's Gland	Adenocarcinoma	1 2	1 2	0 0

Table 39 (continued)

Organ	Lesion	Number of Lesions		
		Control	12.5 mg/kg/d	50 mg/kg/d
		Percent (64)*	Percent (59)	Percent (60)
Muscle	Hemorrhage	1	1	0
		2	2	0
	Inflammation, chronic	0	1	0
		0	2	0
	Mineralization, focal	1	0	0
		2	0	0
	Sarcoma, metastatic	0	0	1
		0	0	2
Ovary	Atrophy	1	1	0
		2	2	0
	Congestion	0	0	1
		0	0	2
	Cyst	8	8	3
		13	14	5
	Inflammation, chronic	0	1	1
		0	2	2
	Inflammation, purulent	1	1	0
		2	2	0
	Necrosis of fat (paraovarian)	2	0	0
		3	0	0
	Pigmentation	0	1	0
		0	2	0
	Vacuolization	1	0	0
		2	0	0
	Adenocarcinoma	1	0	0
		2	0	0

Table 39 (continued)

Organ	Lesion	Number of Lesions		
		Control	12.5 mg/kg/d	50 mg/kg/d
		Percent (64)*	Percent (59)	Percent (60)
Ovary	Adenocarcinoma, metastatic	0	0	1
		0	0	2
	Carcinoma	0	0	1
		0	0	2
	Granulosa, theca cell tumor	1	0	0
		2	0	0
	Leukemia	1	1	0
		2	2	0
	Sarcoma	0	0	2
		0	0	3
Pancreas	Atrophy, focal	11	14	11
		17	24	18
	Cyst	1	0	0
		2	0	0
	Hyperplasia, acinar cell, focal	0	0	1
		0	0	2
	Hyperplasia, islet cell, focal	2	1	1
		3	2	2
	Hyperplasia, ductular	0	0	1
		0	0	2
	Inflammation, chronic focal	13	12	22
		20	20	37
	Inflammation, acute focal	0	1	0
		0	2	0
	Lipidosis	30	21	17
		47	36	28

Table 39 (continued)

Organ	Lesion	Number of Lesions		
		Control	12.5 mg/kg/d	50 mg/kg/d
		Percent (64)*	Percent (59)	Percent (60)
Pancreas	Adenoma, Islet cell	1	0	0
		2	0	0
	Adenocarcinoma, metastatic	0	0	1
		0	0	2
	Leukemia	3	0	0
		5	0	0
	Fibrosarcoma, metastatic	0	0	1
		0	0	2
	Sarcoma, metastatic	0	0	1
		0	0	2
Parathyroid	Hyperplasia	2	2	0
		3	3	0
	Leukemia	0	1	0
		0	2	0
Pituitary	Cyst	12	20	19
		19	34	32
	Hyperplasia, focal	14	13	19
		22	22	32
	Mineralization	0	1	0
		0	2	0
	Pigmentation	0	2	0
		0	3	0
	Adenoma	31	10†	15†
		48	17	25
	Carcinoma	4	4	0
		6	7	0

Table 39 (continued)

Organ	Lesion	Number of Lesions		
		Control	12.5 mg/kg/d	50 mg/kg/d
		Percent (64)*	Percent (59)	Percent (60)
Salivary Gland	Atrophy	0	2	1
		0	3	2
	Ectasia, ductular	3	3	0
		5	5	0
	Hyperplasia, focal mild	3	1	3
		5	2	5
	Hyperplasia, ductular focal	0	0	1
		0	0	2
	Hyperplasia, ductular mucosa, focal	4	1	1
		6	2	2
	Inflammation, chronic focal	3	2	4
		5	3	7
	Lipidosis	5	11	13
		8	19	22
Skin	Hyperplasia, epithelial focal	0	0	2
		0	0	3
	Hyperplasia, sebaceous gland, focal	1	0	0
		2	0	0
	Hemorrhage, focal	1	0	0
		2	0	0
	Inflammation, chronic	1	1	0
		2	2	0
	Keratoacanthoma	1	0	0
		2	0	0
Spinal Cord	Gliosis, focal	0	0	1
		0	0	2
	Hemorrhage, focal	0	1	0
		0	2	0

Table 39 (continued)

Organ	Lesion	Number of Lesions		
		Control Percent (64)*	12.5 mg/kg/d Percent (59)	50 mg/kg/d Percent (60)
Spinal Cord	Vacuolization, gray matter, focal	50 78	36 61	34† 57
	Vacuolization, white matter, focal	54 84	45 76	48 80
Spleen	Hematopoiesis, extramedullary, moderate	7 11	7 12	6 10
	Hyperplasia, granulocytic	0 0	1 2	0 0
	Hyperplasia, plasma cell	0 0	2 3	0 0
	Inflammation, chronic focal	0 0	1 2	0 0
	Necrosis, focal	1 2	1 2	0 0
	Leukemia	14 22	19 32	10 17
Stomach				
Forestomach	Edema	0 0	1 2	0 0
	Hyperplasia, epithelial, mild	5 8	3 5	8 13
	Papilloma	1 2	0 0	1 2
Glandular	Glandular dilation and atrophy	40 63	36 61	47 78
	Inflammation, chronic	1 2	1 2	1 2

Table 39 (continued)

Organ	Lesion	Number of Lesions		
		Control	12.5 mg/kg/d	50 mg/kg/d
		Percent (64)*	Percent (59)	Percent (60)
Stomach				
Glandular	Mineralization, focal	0 0	1 2	0 0
	Necrosis, focal	0 0	1 2	0 0
	Adenocarcinoma	0 0	0 0	1 2
	Leiomyosarcoma	0 0	0 0	1 2
	Leukemia	1 2	0 0	0 0
Thymus	Congestion	0 0	1 2	1 2
	Cyst, focal	0 0	0 0	1 2
	Hemorrhage	1 2	1 2	0 0
	Involution	52 81	47 80	48 80
	Leukemia	0 0	1 2	0 0
	Thymoma	0 0	0 0	1 2
Thyroid	Cyst, focal	1 2	0 0	1 2
	Hyperplasia, C-cell	13 20	14 24	6 10

Table 39 (continued)

Organ	Lesion	Number of Lesions		
		Control	12.5 mg/kg/d	50 mg/kg/d
		Percent (64)*	Percent (59)	Percent (60)
Thyroid	Adenoma, C-cell	3	3	1
		5	5	2
	Carcinoma, C-cell	3	3	5
		5	5	8
	Leukemia	0	1	0
		0	2	0
	Sarcoma, metastatic	0	0	1
		0	0	2
Trachea	Atrophy, mucosa	0	0	1
		0	0	2
	Ectasia, glands	16	17	18
		25	29	30
	Inflammation, chronic focal, mild	7	9	16
		11	15	27
	Sarcoma, metastatic	0	0	1
		0	0	2
Urinary Bladder	Hyperplasia, mucosa	11	7	16
		17	12	27
	Inflammation, chronic	0	5	6†
		0	8	10
	Papilloma	0	2	2
		0	3	3
Uterus	Cyst	11	14	21
		17	24	35
	Hemorrhage	0	0	1
		0	0	2
	Hydrometria	6	17†	7
		9	29	12

Table 39 (concluded)

Organ	Lesion	Number of Lesions		
		Control	12.5 mg/kg/d	50 mg/kg/d
		Percent (64)*	Percent (59)	Percent (60)
Uterus	Hyperplasia, mucosal	0	3	2
		0	5	3
	Inflammation, chronic	0	0	6
		0	0	10
	Inflammation, purulent	0	2	1
		0	3	2
	Adenoma	0	1	1
		0	2	2
	Adenocarcinoma	1	0	1
		2	0	2
	Adenocarcinoma, metastatic	1	0	1
		2	0	2
	Fibroma	0	0	1
		0	0	2
	Myxoma	1	0	0
		2	0	0
	Hemangioma	0	1	1
		0	2	2
	Stromal polyp	21	14	17
		33	24	28
	Stromal sarcoma	2	4	3
		3	8	5
	Tumor, NOS, necrotic	0	1	0
		0	2	0
	Leukemia	1	0	0
		2	0	0

although it was not statistically significant. An increased incidence of marked chronic nephropathy (generalized degenerative change) was also seen in males at the mid-dose level, although it was not statistically significant.

An increased incidence of congestion was seen in the lungs of mid-dose males. This is thought to reflect the increased incidence of early deaths in this group. Increased mild focal mineralization was also seen in this group and is thought to be secondary to renal failure. The minimal to mild increase in pigmented macrophages in the low-dose group is not of biological significance, and probably represents metabolic breakdown products and minute inhaled particulates and is not unusual in aged rats.

In males at the mid-dose level, the decreased incidence of focal atrophy and islet cell hyperplasia of the pancreas, changes due to age,[38,44,45] reflects the large number of early deaths in this group. The increased incidence of mineralization and hyperplasia of the parathyroid in males at this dose level may be secondary to kidney failure.[47]

The decreased incidence of congestion of the pituitary in males at the low-dose level is of uncertain biological significance. In the mid-dose group, the decreased incidence of pituitary adenomas is believed to be attributable to the early deaths in this group, since the incidence of this tumor usually increases with age.[44-46].

The decreased incidence of focal mild hyperplasia of the prostate in the mid-dose males is believed to be due to the early deaths of many of these animals. The increased incidence of inflammation of the prostate at the mid-dose level may be due to the proximity of this organ to the urinary bladder, which showed extensive toxic changes in this group (see below).

The decreased incidence of lipidosis of the salivary gland in the mid-dose males is not biologically significant and is attributed to the large number of early deaths in this group.

Atrophy of the seminal vesicle, an age-related change,[44] decreased in the mid-dose group due to the early deaths. The increased incidence of inflammation in this organ may be related to inflammation of the urinary bladder.

In males at the mid-dose level, the decreased incidence of mild focal vacuolization of the spinal cord, an age-related change of the central nervous system, is believed to be due to the early deaths in this group.

The increased mild lymphoid depletion in the spleen in mid-dose males is believed to be a chemically-induced change.

The increased occurrence in low-dose males of mild epithelial cell hyperplasia and glandular dilation and atrophy of the stomach (usual age-related changes[43]) may be compound-related but the changes were not severe enough to be biologically significant. The mineralization present in males at the mid-dose level is believed to be secondary to kidney damage.[47]

In the low-dose males, the increased incidence of mild focal mineralization of the testes, often an aging change,[36] may be compound-related but is not believed severe enough to be biologically significant. The decreased incidence of interstitial cell tumors in the mid-dose group reflects early mortality.[43,44]

In mid-dose males, the decreased occurrence of ectasia of submucosal glands of the trachea, an aging change,[44] reflects early mortality.

The increased incidence of hemorrhage, mucosal hyperplasia, serosal fibroplasia, inflammation, and necrosis of the urinary bladder in the mid-dose males is biologically significant and appears compound-related. It is believed that these changes, coupled with those in the kidney, were responsible for the many deaths in this group.

Table 39 summarizes microscopic lesions in the females that were found dead on test or were sacrificed when moribund during the second year of the study or that survived until the terminal sacrifice. The statistically increased incidence of granulocytic hyperplasia of the bone marrow in mid-dose females may in part be a response to inflammatory changes present in the urinary bladder in this group.

A decreased incidence of focal hepatocytic cytoplasmic vacuolization of the liver, an aging or metabolic change, was seen in females at the mid-dose level. The reason for this is not apparent but it may be treatment-related.

Females at the mid-dose level showed decreased numbers of small foci of, at times, pigment-laden macrophages in the lung. The cause of this decrease is not readily apparent but it is not biologically significant.[44,45]

The decreased incidences of ductular ectasia and fibroadenoma in the mammary gland in the low- and mid-dose groups appear to be treatment-related, presumably resulting from a pituitary gland hormonal influence.

A decreased incidence of anterior pituitary adenomas was seen in the low- and mid-dose groups and is believed to be treatment-related. This decreased incidence is also reflected in mammary gland changes. As previously mentioned, rat pituitary tumors often produce mammotropic hormones,[44] and there is an association between anterior pituitary tumors and ectatic ducts and fibroadenomas of the mammary gland.[38]

A decreased incidence of mild focal gray matter vacuole formation in the spinal cord, an aging change,[44,48] was seen in mid-dose females. The cause of this decrease is not apparent. Because signs of spinal cord dysfunction were not seen clinically, this finding is not believed to be biologically significant.

The increased incidence of chronic inflammation of the urinary bladder in the low- and mid-dose groups is treatment-related. However, this increase was statistically significant in females only at the mid-dose level.

An increased incidence of hydrometria was seen in the low-dose group, although the biological significance of this uterine condition is uncertain.

In summary, the principal biologically significant, LAP-induced toxic lesions observed in Fischer-344 rats were degenerative changes in the eye and urinary system and decreased cellularity of lymphoid tissue. These changes were generally restricted to the mid- and high-dose groups and were usually more pronounced in male animals.

The histologic changes present in the eye were most prominent in the lens and retina. The lens changes were focal to diffuse subcapsular vacuolization, granularity, mineralization, disruption of lens fibers, and occasional focal proliferation of subcapsular epithelial cells. These lesions are consistent with clinical cataract formation[36,37] and were consistently more severe and extensive than the typical age-related changes[38] seen in control animals.

Retinal lesions consisted of multifocal to diffuse selective destruction of the photoreceptor layers (rods, cones, and outer nuclear layer), with the resulting displacement of the remaining layers. These changes were much more extensive than the mild peripheral retinal degeneration that was present in control and low-dose animals and that are commonly found in old Fischer-344 rats.[39] Other changes present in the eye were inflammation and new blood vessel formation in the cornea and lessened focal mineralization of the sclera.

Lesions present in the kidneys of treated rats consisted of papillary necrosis, hydronephrosis, hyperplasia of the pelvic epithelium, and increased mineralization of the parenchyma. Chronic nephropathy was also more severe in the mid-dose group.

The urinary bladder was extensively damaged in the mid- and high-dose male rats. In addition to necrosis, hemorrhage, and inflammation of all layers of the bladder wall, mucosal hyperplasia and serosal fibroplasia were present. The inflammation also commonly extended to the adjacent prostate and seminal vesicle.

Lymphoid depletion was commonly seen in the hematopoietic system, especially the spleen and thymus, in high-dose male rats that died during the course of this experiment. This condition was occasionally present to a lesser degree and extent in high-dose males that were sacrificed and in other groups.

A physiological change typically observed in the livers of treated animals was a slight expansion and lighter histologic staining of hepatocyte cytoplasm. This is believed to reflect subcellular adaptation for metabolism of LAP.[42,49]

Water Quality Criteria

From the results of the chronic study, an Acceptable Daily Intake (ADI) for LAP was estimated according to the National Research Council recommendations for chronic nonhuman toxicity data with no indication of

carcinogenicity.[50] The ADI was calculated using a no-observed-adverse-effect-level (NOAEL) of 12.5 mg/kg/day, a safety factor of 100, and an average body weight of 70 kg, as follows:

$$ADI = \frac{12.5 \text{ mg/kg} \times 70 \text{ kg}}{100} = 8.75 \text{ mg}$$

To provide an estimated level of human health protection from the toxic properties of LAP ingested through water or contaminated aquatic organisms, a water quality criterion (C) was determined. Standard daily exposure assumptions of 2 liters of water and 6.5 grams of edible aquatic products were used, based on a weighted average of 3% lipids for freshwater and estuarine fish and shellfish in the average diet.[51] A bioconcentration factor (BCF) was used to relate pollutant residues in aquatic organisms to the pollutant concentration in ambient waters in which they reside. For LAP, a BCF of 20.5 L/kg has been estimated for aquatic organisms containing approximately 7.6% lipids.[52] The weighted average BCF was calculated as follows:

$$20.5 \text{ L/kg} \times \frac{3.0\%}{7.6\%} = 8.1 \text{ L/kg}$$

Based on these data and assumptions, the ambient water quality criterion for LAP was calculated as follows:

$$C = \frac{8.75 \text{ mg}}{2 \text{ L} + (0.0065 \text{ kg} \times 8.1 \text{ L/kg})} = 4.26 \text{ mg/L}$$

It should be noted that this calculation does not provide an estimate for exposure to LAP through non-fish dietary intake or through inhalation. Therefore, it would be inappropriate to use this value as a maximum concentration level. It does, however, provide an estimate of a safe level of exposure to LAP for an adult male through ingestion of water or aquatic organisms.

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Appendix A

AVERAGE WEEKLY DOSE RECEIVED (mg/kg/day), PERCENTAGE OF INTENDED DOSE, AND CUMULATIVE WEEKLY DOSE RECEIVED FOR MALE RATS TREATED WITH LAP*

	12.5 mg/kg/day			50 mg/kg/day			200 mg/kg/day†		
Week	Dose Received	% of Intended	Cumulative Dose	Dose Received	% of Intended	Cumulative Dose	Dose Received	% of Intended	Cumulative Dose
1	11.85	94.7	--	43.36	86.7	--	98.21	49.1	--
2	9.94	79.5	10.89	39.33	78.7	41.35	172.41	86.2	135.31
3	12.06	96.5	11.28	47.86	95.7	43.52	175.67	87.8	148.76
4	11.09	88.7	11.23	46.80	93.6	44.34	183.82	91.9	157.53
5	12.25	98.0	11.44	47.86	95.7	45.04	188.80	94.4	163.78
6	11.40	91.2	11.43	45.86	91.7	45.18	185.71	92.9	167.44
7	12.96	103.7	11.65	51.27	102.5	46.05	232.58	116.3	176.75
8	11.94	95.5	11.69	47.37	94.7	46.22	220.69	110.3	182.24
9	12.53	100.2	11.78	48.39	96.8	46.46	206.70	103.4	184.99
10	12.14	97.1	11.82	46.47	92.9	46.46	194.07	97.0	185.87
11	12.06	96.5	11.84	48.35	96.7	46.63	200.36	100.2	187.19
12	12.16	97.3	11.87	47.83	95.7	46.73	201.06	100.5	188.35
13	12.55	100.4	11.92	50.52	101.0	47.02	112.51	112.51	182.52
14	11.86	94.9	11.92	48.83	97.7	47.15	106.40	106.40	177.08
15	12.50	100.0	11.96	52.16	104.3	47.48	105.13	105.10	172.28

* Assuming 100% of the compound available in the diet.

† Dose level reduced to 100 mg/kg/day starting with Week 13.

Appendix A (continued)

Week	12.5 mg/kg/day			50 mg/kg/day			100 mg/kg/day		
	Dose Received	% of Intended	Cumulative Dose	Dose Received	% of Intended	Cumulative Dose	Dose Received	% of Intended	Cumulative Dose
16	12.64	101.1	12.00	51.22	102.4	47.71	114.25	114.3	168.65
17	13.35	106.8	12.08	52.75	105.5	48.01	119.78	119.8	165.78
18	12.85	102.8	12.12	51.92	103.8	48.23	112.50	112.5	162.82
19	12.94	103.5	12.17	54.14	108.3	48.54	112.03	112.0	160.15
20	12.65	101.2	12.19	53.99	108.0	48.81	108.12	108.1	157.55
21	12.96	103.7	12.23	57.17	114.3	49.21	109.57	109.6	155.26
22	12.64	101.1	12.25	57.32	114.6	49.58	107.43	107.4	153.09
23	12.47	99.8	12.26	52.03	104.1	49.69	105.91	105.9	151.04
24	13.07	104.6	12.29	57.53	115.1	50.02	102.64	102.6	149.02
25	12.79	102.3	12.31	52.65	105.3	50.13	101.89	101.9	147.13
26	12.70	101.6	12.33	53.20	106.4	50.25	107.56	107.6	145.61
27	12.42	99.4	12.33	54.03	108.1	50.39	101.56	101.6	143.98
28	11.60	92.8	12.30	51.69	103.4	50.44	104.76	104.8	142.58
29	12.97	103.8	12.33	47.54	95.1	50.34	108.74	108.7	141.41
30	11.83	94.6	12.31	47.54	95.1	50.25	99.31	99.3	140.01
31	12.30	98.4	12.31	49.72	99.4	50.23	99.34	99.3	138.70
32	12.01	96.1	12.30	47.34	94.7	50.14	86.77	86.8	137.08
33	13.19	105.5	12.33	50.36	100.7	50.15	98.09	98.1	135.90

Appendix A (continued)

Week	12.5 mg/kg/day			50 mg/kg/day			100 mg/kg/day		
	Dose Received	% of Intended	Cumulative Dose	Dose Received	% of Intended	Cumulative Dose	Dose Received	% of Intended	Cumulative Dose
34	12.08	96.6	12.32	47.56	95.1	50.07	--*	--	--
35	12.49	99.9	12.32	50.90	101.8	50.09			
36	12.21	97.7	12.32	50.04	100.1	50.09			
37	13.39	107.1	12.35	52.97	105.9	50.17			
38	12.18	97.4	12.35	50.52	101.0	50.18			
39	12.61	100.9	12.36	56.47	112.9	50.34			
40	12.41	99.3	12.36	56.57	113.1	50.50			
41	12.62	101.0	12.37	52.72	105.4	50.55			
42	12.12	97.0	12.36	52.72	105.4	50.60			
43	12.51	100.1	12.36	54.59	109.2	50.69			
44	12.49	99.9	12.36	52.27	104.5	50.73			
45	12.57	100.6	12.36	49.06	98.1	50.69			
46	12.28	98.2	12.36	45.40	90.8	50.58			
47	12.52	100.1	12.36	47.13	94.3	50.51			
48	12.61	100.9	12.37	46.88	93.8	50.43			
49	12.46	99.7	12.37	50.00	100.0	50.42			
50	12.10	96.8	12.36	48.83	97.7	50.39			
51	12.67	101.4	12.37	51.68	103.4	50.42			
52	12.28	98.2	12.37	52.58	105.2	50.46			

* High dose terminated after 33 weeks on test.

Appendix A (continued)

Week	12.5 mg/kg/day			50 mg/kg/day			100 mg/kg/day		
	Dose Received	% of Intended	Cumulative Dose	Dose Received	% of Intended	Cumulative Dose	Dose Received	% of Intended	Cumulative Dose
53	12.41	99.3	12.37	48.30	96.6	50.42	--*	--	--
54	12.26	98.1	12.37	47.80	95.6	50.37			
55	12.11	96.9	12.37	46.99	94.0	50.31			
56	11.07	88.6	12.35	46.85	93.7	50.25			
57	12.67	101.4	12.36	50.86	101.7	50.26			
58	12.18	97.4	12.36	48.77	97.5	50.23			
59	12.49	99.9	12.36	48.45	96.9	50.20			
60	12.22	97.8	12.36	49.51	99.0	50.19			
61	12.71	101.7	12.37	51.39	102.8	50.21			
62	12.24	97.9	12.37	53.27	106.5	50.26			
63	12.22	97.8	12.37	48.14	96.3	50.23			
64	12.41	99.3	12.37	52.23	104.5	50.26			
65	12.50	100.0	12.37	49.34	98.7	50.25			
66	12.40	99.2	12.37	50.83	101.7	50.25			
67	12.12	97.0	12.37	49.86	99.7	50.25			
68	12.37	99.0	12.37	49.07	98.1	50.23			
69	12.93	103.4	12.38	49.56	99.1	50.22			
70	12.55	100.4	12.38	50.63	101.3	50.23			
71	12.65	101.2	12.38	47.79	95.6	50.20			
72	12.32	98.6	12.38	48.85	97.7	50.18			

* High dose terminated after 33 weeks on test.

Appendix A (continued)

Week	12.5 mg/kg/day			50 mg/kg/day			100 mg/kg/day		
	Dose Received	% of Intended	Cumulative Dose	Dose Received	% of Intended	Cumulative Dose	Dose Received	% of Intended	Cumulative Dose
73	12.49	99.9	12.38	48.59	97.2	50.16	--*	--	--
74	12.60	100.8	12.38	48.51	97.0	50.14			
75	12.52	100.2	12.38	48.79	97.6	50.12			
76	12.70	101.6	12.38	50.17	100.3	50.12			
77	12.70	101.6	12.38	50.00	100.0	50.12			
78	12.09	96.7	12.38	48.26	96.5	50.10			
79	12.29	98.3	12.38	48.97	97.9	50.09			
80	12.09	96.7	12.38	49.51	99.0	50.08			
81	12.34	98.7	12.38	51.21	102.4	50.09			
82	11.90	95.2	12.37	49.84	99.7	50.09			
83	12.36	98.9	12.37	53.53	107.0	50.13			
84	11.97	95.8	12.37	50.24	100.5	50.13			
85	12.67	101.4	12.37	49.64	99.3	50.12			
86	12.38	99.0	12.37	49.61	99.2	50.11			
87	12.87	103.0	12.38	49.33	98.7	50.10			
88	12.60	100.8	12.38	49.36	98.7	50.09			
89	12.67	101.4	12.38	47.08	94.2	50.06			
90	12.33	98.6	12.38	46.48	93.0	50.02			

* High dose terminated after 33 weeks on test.

Appendix A (concluded)

Week	12.5 mg/kg/day			50 mg/kg/day			100 mg/kg/day		
	Dose Received	% of Intended	Cumulative Dose	Dose Received	% of Intended	Cumulative Dose	Dose Received	% of Intended	Cumulative Dose
91	13.77	110.2	12.40	51.09	102.2	50.03	--*	--	--
92	13.54	108.3	12.41	53.85	107.7	50.07			
93	13.04	104.3	12.42	48.90	97.8	50.06			
94	12.38	99.0	12.42	49.22	98.4	50.05			
95	12.29	98.3	12.42	49.62	99.2	50.05			
96	12.16	97.3	12.42	49.46	98.9	50.04			
97	12.65	101.2	12.42	48.81	97.6	50.03			
98	12.06	96.5	12.42	49.30	98.6	50.02			
99	12.34	98.7	12.42	54.96	109.9	50.07			
100	12.48	99.8	12.42	53.50	107.0	50.10			
101	12.86	102.9	12.42	50.75	101.5	50.11			
102	11.53	92.2	12.41	49.24	98.5	50.10			
103	12.26	98.1	12.41	54.67	109.3	50.14			
104	11.87	95.0	12.40	47.11	94.2	50.11			

* High dose terminated after 33 weeks on test.

Appendix B

AVERAGE WEEKLY DOSE RECEIVED (mg/kg/day), PERCENTAGE OF INTENDED DOSE, AND CUMULATIVE WEEKLY DOSE RECEIVED FOR FEMALE RATS TREATED WITH LAP*

	12.5 mg/kg/day			50 mg/kg/day			200 mg/kg/day†		
Week	Dose Received	% of Intended	Cumulative Dose	Dose Received	% of Intended	Cumulative Dose	Dose Received	% of Intended	Cumulative Dose
1	11.40	91.2	--	41.92	83.8	--	101.12	50.6	--
2	8.74	69.9	10.07	35.19	70.4	38.56	157.78	78.9	129.45
3	11.40	91.2	10.51	45.38	90.8	40.83	188.78	94.4	149.23
4	10.89	87.1	10.61	42.78	85.6	41.32	195.75	97.9	160.86
5	12.08	96.6	10.90	43.43	86.9	41.74	194.21	97.1	167.53
6	10.66	85.3	10.86	42.74	85.5	41.91	185.21	92.6	170.48
7	11.49	91.9	10.95	51.14	102.3	43.23	216.69	108.3	177.08
8	10.53	84.2	10.90	47.73	95.5	43.79	203.64	101.8	180.40
9	12.12	97.0	11.04	49.87	99.7	44.47	207.88	103.9	183.45
10	11.83	94.6	11.12	47.90	95.8	44.81	197.78	98.9	184.88
11	10.46	83.7	11.01	47.78	93.8	44.08	233.33	116.7	189.28
12	10.45	83.6	11.01	46.90	93.8	45.23	219.87	109.9	191.83
13	11.99	95.9	11.08	50.73	101.5	45.65	123.68	123.7	186.59
14	11.24	89.9	11.10	49.29	98.6	45.91	104.82	104.8	180.75
15	12.23	105.8	11.24	50.63	101.3	46.23	103.35	103.4	175.59

* Assuming 100% of the compound available in the diet.

† Dose level reduced to 100 mg/kg/day starting with Week 13.

Appendix B (continued)

Week	12.5 mg/kg/day			50 mg/kg/day			100 mg/kg/day		
	Dose Received	% of Intended	Cumulative Dose	Dose Received	% of Intended	Cumulative Dose	Dose Received	% of Intended	Cumulative Dose
16	13.15	105.2	11.36	50.73	101.5	46.51	106.43	106.4	171.27
17	13.49	107.9	11.49	50.53	101.1	46.75	105.65	105.7	167.41
18	12.90	103.2	11.57	50.24	100.5	46.94	100.95	101.0	163.71
19	12.36	98.9	11.61	52.10	104.2	47.21	102.59	102.6	160.50
20	12.04	96.3	11.63	50.42	100.8	47.37	97.27	97.3	157.34
21	12.56	100.5	11.67	49.33	98.7	47.46	105.32	105.3	154.86
22	12.49	99.9	11.71	51.50	103.0	47.64	103.78	103.8	152.54
23	12.12	97.0	11.73	49.02	98.0	47.70	100.96	101.0	150.30
24	11.74	93.9	11.73	48.21	96.4	47.72	105.75	105.8	148.44
25	12.11	96.9	11.75	49.45	98.9	47.79	100.74	100.7	146.53
26	13.21	105.7	11.80	46.99	94.0	47.76	101.10	101.1	144.78
27	11.84	94.7	11.80	49.16	98.3	47.81	103.05	103.0	143.23
28	11.78	94.2	11.80	47.81	95.6	47.81	106.45	106.5	141.92
29	13.72	109.8	11.87	48.26	96.5	47.83	102.68	102.7	140.57
30	11.90	95.2	11.87	47.74	95.5	47.83	100.92	100.9	139.25
31	12.23	97.8	11.88	48.69	97.4	47.86	102.18	102.2	138.05
32	12.10	96.8	11.89	48.12	96.2	47.87	99.20	99.2	136.84
33	13.60	108.8	11.94	51.09	102.2	47.97	99.61	99.6	135.71

Appendix B (continued)

Week	12.5 mg/kg/day			50 mg/kg/day			100 mg/kg/day		
	Dose Received	% of Intended	Cumulative Dose	Dose Received	% of Intended	Cumulative Dose	Dose Received	% of Intended	Cumulative Dose
34	11.77	94.2	11.94	50.56	101.1	48.05	--*	--	--
35	12.88	103.0	11.97	53.30	106.6	48.20			
36	12.00	96.0	11.97	51.07	102.1	48.28			
37	13.69	109.5	12.02	53.53	107.1	48.42			
38	12.03	96.2	12.02	52.43	105.1	48.53			
39	12.55	100.4	12.03	54.18	108.4	48.67			
40	12.42	99.4	12.04	53.91	107.8	48.81			
41	12.78	102.2	12.06	54.28	108.6	48.94			
42	12.08	96.6	12.06	51.14	102.3	48.99			
43	12.66	101.3	12.07	49.95	99.9	49.01			
44	12.60	100.8	12.08	50.72	101.4	49.05			
45	12.74	101.9	12.09	49.50	99.0	49.06			
46	12.74	101.9	12.10	49.76	99.5	49.08			
47	12.68	101.5	12.11	50.71	101.4	49.11			
48	12.93	103.4	12.13	51.99	104.0	49.17			
49	12.21	97.6	12.13	49.50	99.0	49.18			
50	11.97	95.8	12.13	52.01	104.0	49.24			
51	12.47	99.8	12.14	51.53	103.1	49.28			
52	12.28	98.2	12.14	49.38	98.8	49.28			

* High dose terminated after 33 weeks on test.

Appendix B (continued)

Week	12.5 mg/kg/day			50 mg/kg/day			100 mg/kg/day		
	Dose Received	% of Intended	Cumulative Dose	Dose Received	% of Intended	Cumulative Dose	Dose Received	% of Intended	Cumulative Dose
53	12.52	100.2	12.15	51.57	103.1	49.32	--*	--	--
54	12.24	97.9	12.15	49.46	98.9	49.32			
55	12.28	98.2	12.15	48.27	96.5	49.30			
56	11.86	94.9	12.14	47.58	95.2	49.27			
57	12.57	100.6	12.15	49.20	98.4	49.27			
58	12.25	98.0	12.15	49.02	98.0	49.27			
59	12.46	99.7	12.16	49.74	99.5	49.28			
60	12.61	100.4	12.17	50.73	101.5	49.30			
61	13.00	104.0	12.18	50.95	101.9	49.33			
62	12.52	100.2	12.19	50.04	100.1	49.34			
63	13.03	104.2	12.20	49.59	99.2	49.34			
64	12.86	102.9	12.21	51.28	102.6	49.37			
65	12.54	100.3	12.22	47.62	95.2	49.34			
66	12.19	97.5	12.21	49.06	98.1	49.34			
67	12.64	101.1	12.22	50.31	100.6	49.35			
68	12.47	99.8	12.22	49.15	98.3	49.35			
69	12.94	103.5	12.23	52.26	104.5	49.39			
70	12.53	100.2	12.23	48.22	96.4	49.37			
71	12.55	100.4	12.23	51.10	102.2	49.39			
72	12.21	97.7	12.23	48.51	97.0	49.38			

* High dose terminated after 33 weeks on test.

Appendix B (continued)

Week	12.5 mg/kg/day			50 mg/kg/day			100 mg/kg/day		
	Dose Received	% of Intended	Cumulative Dose	Dose Received	% of Intended	Cumulative Dose	Dose Received	% of Intended	Cumulative Dose
73	12.82	102.6	12.24	50.68	101.4	49.40	--*	--	--
74	12.49	99.9	12.24	49.47	98.9	49.40			
75	12.22	97.8	12.24	48.73	97.5	49.39			
76	12.48	99.8	12.24	53.77	107.5	49.45			
77	12.64	101.1	12.25	51.61	103.2	49.48			
78	12.40	99.2	12.25	51.41	102.8	49.50			
79	12.54	100.3	12.25	50.04	100.1	49.51			
80	12.26	98.1	12.25	50.52	101.0	49.52			
81	12.84	102.7	12.26	50.33	100.7	49.53			
82	12.27	98.2	12.26	49.19	98.4	49.53			
83	12.58	100.6	12.26	50.55	101.1	49.54			
84	12.48	99.8	12.26	51.97	103.9	49.57			
85	12.40	99.2	12.26	49.62	99.2	49.57			
86	12.24	97.9	12.26	50.09	100.2	49.58			
87	13.21	105.7	12.27	51.94	103.9	49.61			
88	12.22	97.8	12.27	51.73	103.5	49.63			
89	11.55	92.4	12.26	48.67	97.3	49.62			
90	10.91	87.3	12.25	48.95	97.9	49.61			

* High dose terminated after 33 weeks on test.

Appendix B (concluded)

Week	12.5 mg/kg/day			50 mg/kg/day			100 mg/kg/day		
	Dose Received	% of Intended	Cumulative Dose	Dose Received	% of Intended	Cumulative Dose	Dose Received	% of Intended	Cumulative Dose
91	13.27	106.2	12.26	54.84	109.7	47.67	—*	--	--
92	13.71	109.7	12.28	55.10	110.2	49.73			
93	12.93	103.4	12.29	51.13	102.3	49.75			
94	12.48	99.8	12.29	51.60	103.2	49.77			
95	12.22	97.8	12.29	51.89	103.8	49.79			
96	12.13	97.0	12.29	52.15	104.3	49.81			
97	12.98	103.8	12.30	50.64	101.3	49.82			
98	12.39	99.1	12.30	48.83	97.7	49.81			
99	13.16	105.3	12.31	51.30	102.6	49.83			
100	12.70	101.6	12.31	51.95	103.9	49.85			
101	13.08	104.6	12.32	50.61	101.2	49.86			
102	12.16	97.3	12.32	51.06	102.1	49.87			
103	12.78	102.2	12.32	47.69	95.4	49.85			
104	11.83	94.6	12.32	47.88	95.8	49.83			

* High dose terminated after 33 weeks on test.

Appendix C

ANALYSES OF DIET PREPARATION OF LAP

Week of Study	Dose Level (mg/kg/day)	Sex	LAP Concentration (ppm) Intended	LAP Concentration (ppm) Actual	Percent Change from Intended	Concentration (mg/L) TNT	Concentration (mg/L) RDX	TNT/RDX Ratio
1 and 2	12.5	M & F	125	110	-12.0	18.0	9.4	1.91
	50.0	M & F	500	476	- 4.8	75.3	43.8	1.72
	200.0	M & F	2000	1844	- 7.8	288.0	173.0	1.66
3 and 4	12.5	Male	145	130*	-10.7	20.1	11.5	1.75
		Female	132	110*	-16.9	17.5	9.5	1.83
	50.0	Male	585	548*	- 6.3	85.9	52.8	1.63
		Female	540	471*	-12.9	72.9	44.0	1.66
	200.0	Male	2200	2111*	- 4.0	319.7	211.3	1.52
		Female	2500	2471*	- 1.1	361.0	245.9	1.47
5 and 6	12.5	Male	169	148	-12.2	23.4	13.8	1.70
		Female	146	129	-11.9	20.0	11.6	1.72
	50.0	Male	685	643	- 6.1	96.7	60.1	1.61
		Female	595	566	- 4.9	86.9	54.1	1.61
	200.0	Male	2600	2609	+ 0.4	379.1	270.0	1.40
		Female	2700	2574	- 4.7	372.7	252.5	1.48
7 and 8	12.5	Male	200	185	- 7.4	27.7	17.5	1.58
		Female	165	154	- 6.7	23.3	15.1	1.55
	50.0	Male	800	768	- 4.0	121.1	72.2	1.68
		Female	775	757	- 2.4	115.6	74.3	1.56
	200.0	M & F	3200	3089	- 3.5	443.6	305.9	1.45
9 and 10	12.5	Male	220	208	- 5.5	32.1	21.1	1.53
		Female	188	180	- 4.0	28.5	18.5	1.54
	50.0	Male	875	897	+ 2.5	138.8	89.4	1.55
		Female	800	814	+ 1.7	121.9	81.5	1.50
	200.0	M & F	3200	2996*	- 6.4	452.8	293.1	1.55

*Average of two or three analyses.

Appendix C (continued)

Week of Study	Dose Level (mg/kg/day)	Sex	LAP Concentration (ppm) Intended	LAP Concentration (ppm) Actual	Percent Change from Intended	Concentration (mg/L) TNT	Concentration (mg/L) RDX	TNT/RDX Ratio
11 and 12	12.5	Male	235	222	- 5.7	34.9	21.1	1.66
		Female	181	166	- 8.5	25.8	15.6	1.65
	50.0	Male	950	878	- 7.6	133.1	86.8	1.53
		Female	840	797	- 5.1	124.8	77.0	1.62
	200.0	Male	3200	3020	- 5.6	462.6	296.4	1.56
		Female	3500	3279	- 6.3	528.8	292.6	1.81
13 and 14	12.5	Male	255	233	- 8.8	37.4	22.8	1.64
		Female	220	221	+ 0.6	35.4	21.7	1.63
	50.0	Male	1035	974	- 5.9	152.9	92.1	1.66
		Female	900	830	- 7.8	122.0	77.7	1.57
	100.0	Male	1670	1634	- 2.2	236.6	149.3	1.58
		Female	1800	1715	- 4.7	279.0	165.2	1.69
23 and 24	12.5	Male	280	248	-11.5	38.1	23.0	1.66
		Female	245	228	- 6.8	36.2	21.3	1.70
	50.0	Male	1050	1004	- 4.4	149.9	90.4	1.66
		Female	975	951	- 2.5	158.0	88.3	1.79
	100.0	Male	1750	1570	-10.3	239.1	140.9	1.70
		Female	1875	1788	- 4.6	292.4	167.2	1.75
35 and 36	12.5	Male	310	289	- 6.8	46.0	28.2	1.63
		Female	264	248*	- 6.0	46.1	28.7	1.61
	50.0	Male	1047	961	- 8.2	190.8	117.9	1.62
		Female	1100	1028	- 6.5	164.4	103.5	1.59
49 and 50	12.5	Male	325	281*	-13.6	44.2	25.3	1.75
		Female	270	258*	- 4.3	47.3	27.4	1.73
	50.0	Male	1000	913*	- 8.7	150.4	87.9	1.71
		Female	1060	1009*	- 4.8	151.4	89.2	1.70

*Average of two or three analyses.

Appendix C (concluded)

Week of Study	Dose Level (mg/kg/day)	Sex	LAP Concentration (ppm) Intended	LAP Concentration (ppm) Actual	Percent Change from Intended	Concentration (mg/L) TNT	Concentration (mg/L) RDX	TNT/RDX Ratio
59 and 60	12.5	Male	335	330	- 1.5	55.6	33.4	1.66
		Female	290	291	+ 0.3	50.1	30.6	1.64
	50.0	Male	1040	1022	- 1.7	160.8	95.8	1.68
		Female	1100	1160	+ 5.4	180.1	99.5	1.64
71 and 72	12.5	Male	350	297	-15.1	51.1	27.7	1.85
		Female	300	263	-12.3	46.1	23.7	1.94
	50.0	Male	1070	886	-17.2	116.4	70.3	1.66
		Female	1170	1075	- 8.1	166.4	99.5	1.67
85 and 86	12.5	Male	365	338	- 7.3	52.5	32.1	1.63
		Female	320	299	- 6.6	46.9	27.8	1.69
	50.0	Male	1110	1005	- 9.5	154.9	96.3	1.61
		Female	1205	1175	- 2.5	179.3	114.5	1.57
95 and 96	12.5	Male	345	330	- 4.3	52.1	30.5	1.71
		Female	320	313	- 2.3	49.0	29.2	1.68
	50.0	Male	1115	1090	- 2.2	169.6	102.9	1.65
		Female	1200	1193	- 0.6	185.2	113.1	1.64

APPENDIX D

AVERAGE WEEKLY FOOD CONSUMPTION (G/DAY) OF MALE RATS
TREATED WITH BAP

DEPENDENT VARIABLE	CONTROL	TREATMENT GROUPS 12.5 MG/KG	W	50 MG/KG	W	200 MG/KG	W
WEEK 1	12.9 + .171 (15)	12.6 + .215 (14)		11.1 + .216 (14)	*	5.5 + .189 (14)	*
WEEK 2	13.9 + .127 (15)	12.8 + .319 (14)		11.8 + .401 (14)	*	10.0 + .269 (14)	*
WEEK 3	15.9 + .135 (15)	15.8 + .134 (14)		14.4 + .131 (14)	*	10.7 + .139 (14)	*
WEEK 4	17.8 + .383 (15)	16.6 + .298 (14)		16.0 + .409 (14)		12.7 + .270 (14)	*
WEEK 5	18.1 + .243 (15)	17.1 + .195 (14)		15.3 + .228 (14)	*	12.2 + .247 (14)	*
WEEK 6	18.1 + .250 (15)	17.0 + .196 (14)		15.6 + .204 (14)	*	13.0 + .276 (14)	*
WEEK 7	17.9 + .230 (15)	17.3 + .283 (14)		15.7 + .240 (14)	*	14.1 + .498 (14)	*
WEEK 8	16.5 + .158 (15)	16.6 + .197 (14)		15.1 + .421 (14)		14.0 + .444 (14)	*
WEEK 9	16.7 + .135 (15)	16.4 + .210 (14)		14.6 + .219 (14)	*	13.5 + .388 (13)†	*
WEEK 10	16.9 + .155 (15)	16.5 + .181 (14)		14.5 + .296 (14)	*	13.1 + .364 (14)	*
WEEK 11	16.3 + .138 (15)	15.8 + .182 (14)		14.3 + .193 (14)	*	13.9 + .433 (14)	*
WEEK 12	17.0 + .111 (15)	16.3 + .211 (14)		14.5 + .271 (14)	*	14.2 + .432 (14)	*

ENTRIES ARE MEANS AND STANDARD ERRORS WITH N OF CAGES IN PARENTHESES
W = WILLIAMS TEST OF SIGNIFICANT CONTROL-TREATMENT DIFFERENCES
* CONFIDENCE LEVEL = .95
† ONE CAGE NOT INCLUDED IN AVERAGE BECAUSE OF WET FEED.

APPENDIX D (CONTINUED)

DEPENDENT VARIABLE	TREATMENT GROUPS					
	CONTROL	12.5 MG/KG	W	50 MG/KG	W	100 MG/KG †	W
WEEK 13	16.3 + .114 (15)	15.9 + .203 (14)		14.4 + .181 (14)	*	15.9 + .285 (14)	*
WEEK 14	16.7 + .213 (15)	15.4 + .118 (14)		14.2 + .142 (14)	*	15.8 + .428 (14)	*
WEEK 15	17.5 + .141 (15)	16.2 + .162 (14)		14.8 + .265 (14)	*	15.5 + .390 (14)	*
WEEK 16	17.6 + .097 (15)	16.6 + .157 (14)		14.7 + .223 (14)	*	17.3 + .319 (14)	*
WEEK 17	17.5 + .094 (15)	16.8 + .279 (14)		15.1 + .267 (14)		18.1 + .342 (14)	
WEEK 18	16.8 + .167 (15)	16.4 + .176 (14)		15.1 + .218 (14)		17.5 + .336 (14)	
WEEK 19	17.3 + .136 (15)	16.8 + .244 (14)		15.8 + .253 (14)		17.8 + .493 (14)	
WEEK 20	17.6 + .132 (15)	16.7 + .175 (14)		16.0 + .277 (14)		17.6 + .330 (14)	
WEEK 21	18.2 + .085 (15)	17.3 + .214 (14)		17.1 + .365 (14)		19.4 + .475 (14)	
WEEK 22	17.8 + .179 (15)	17.1 + .241 (14)		17.3 + .354 (14)		19.4 + .417 (14)	*
WEEK 23	17.0 + .314 (15)	16.7 + .423 (14)		16.5 + .316 (14)		18.7 + .668 (14)	
WEEK 24	17.8 + .162 (15)	17.6 + .287 (14)		18.3 + .412 (14)		18.3 + .722 (14)	

ENTRIES ARE MEANS AND STANDARD ERRORS WITH N OF CASES IN PARENTHESES
W = WILLIAMS TEST OF SIGNIFICANT CONTROL-TREATMENT DIFFERENCES
* CONFIDENCE LEVEL = .95
† DOSE LEVEL REDUCED TO 100 MG/KG/DAY STARTING WITH WEEK 13.

APPENDIX D (CONTINUED)

DEPENDENT VARIABLE	CONTROL	TREATMENT GROUPS 12.5 MG/KG	W	50 MG/KG	W	100 MG/KG †	W
WEEK 25	18.4 + .186 (15)	17.2 + .389 (14)		17.9 + .403 (14)		19.0 + .780 (14)	
WEEK 26	18.3 + .223 (15)	17.3 + .263 (14)		18.3 + .402 (14)		20.5 + 1.03 (12) †	
WEEK 27	18.2 + .266 (15)	17.0 + .280 (14)		18.6 + .384 (14)		19.1 + .768 (13)	
WEEK 28	16.6 + .167 (15)	16.0 + .241 (14)		18.0 + .357 (14)		20.0 + .864 (13)	*
WEEK 29	18.1 + .202 (15)	17.8 + .125 (14)		17.3 + .384 (14)		20.6 + .628 (13)	*
WEEK 30	17.1 + .154 (15)	16.4 + .202 (14)		17.4 + .289 (14)		19.2 + .498 (13)	*
WEEK 31	16.9 + .152 (15)	16.6 + .239 (14)		17.7 + .357 (14)		19.7 + .565 (13)	*
WEEK 32	16.8 + .214 (15)	16.3 + .133 (14)		16.9 + .349 (14)		17.5 + 1.21 (13)	
WEEK 33	18.2 + .168 (15)	17.4 + .167 (14)		17.9 + .317 (14)		19.3 + .649 (12)	
WEEK 34	17.3 + .207 (15)	16.1 + .193 (14)		17.0 + .434 (14)			
WEEK 35	17.6 + .146 (15)	16.8 + .263 (14)		17.6 + .339 (14)			
WEEK 36	17.5 + .179 (15)	16.5 + .190 (14)		17.3 + .391 (14)			

ENTRIES ARE MEANS AND STANDARD ERRORS WITH N OF CAGES IN PARENTHESES
W = WILLIAMS TEST OF SIGNIFICANT CONTROL-TREATMENT DIFFERENCES
* CONFIDENCE LEVEL = .95
† HIGH DOSE TERMINATED AFTER 33 WEEKS ON TEST.
‡ ONE CAGE NOT INCLUDED IN AVERAGE BECAUSE OF WET FEED.

DEPENDENT VARIABLE	TREATMENT GROUPS: CONTROL	12.5 MG/KG	W	50 MG/KG	W
WEEK 37	18.9 + .109 (15)	17.9 + .224 (14)		18.3 + .444 (14)	
WEEK 38	17.5 + .220 (15)	16.4 + .190 (14)		17.5 + .370 (14)	
WEEK 39	17.7 + .162 (15)	17.1 + .181 (14)		19.9 + .372 (14)	*
WEEK 40	17.8 + .138 (15)	16.9 + .228 (14)		20.1 + .415 (14)	*
WEEK 41	17.6 + .131 (15)	17.0 + .213 (14)		19.4 + .537 (14)	*
WEEK 42	17.2 + .123 (15)	16.4 + .191 (14)		19.4 + .268 (14)	*
WEEK 43	17.5 + .248 (15)	17.0 + .173 (14)		20.2 + .328 (14)	*
WEEK 44	17.4 + .135 (15)	17.1 + .177 (14)		19.6 + .440 (14)	*
WEEK 45	18.1 + .172 (15)	17.4 + .185 (14)		20.1 + .454 (14)	*
WEEK 46	17.9 + .183 (15)	17.0 + .229 (14)		18.8 + .354 (13)†	
WEEK 47	18.1 + .170 (15)	17.1 + .143 (14)		19.1 + .358 (14)	
WEEK 48	18.0 + .149 (15)	17.3 + .225 (14)		19.0 + .414 (14)	

ENTRIES ARE MEANS AND STANDARD ERRORS WITH N OF CASES IN PARENTHESES
W = WILLIAMS TEST OF SIGNIFICANT CONTROL-TREATMENT DIFFERENCES
* CONFIDENCE LEVEL = .95
† FOOD CONSUMPTION WAS NOT CALCULATED FOR ONE CAGE BECAUSE ONE RAT DIED AND THE TIME OF DEATH COULD NOT BE DETERMINED.

APPENDIX D (CONTINUED)

DEPENDENT VARIABLE	TREATMENT GROUPS			
	CONTROL	12.5 MG/KG	W	50 MG/KG	W
WEEK 49	17.5 + .175 (15)	17.1 + .214 (14)		19.2 + .444 (14)	*
WEEK 50	17.4 + .129 (15)	16.6 + .344 (14)		18.8 + .304 (14)	
WEEK 51	18.0 + .156 (15)	17.5 + .157 (14)		20.0 + .371 (14)	*
WEEK 52	17.8 + .197 (15)	17.0 + .226 (14)		20.4 + .465 (14)	*
WEEK 53	17.5 + .288 (13)	17.0 + .176 (12)		18.7 + .352 (12)	
WEEK 54	17.7 + .176 (13)	16.9 + .200 (12)		18.6 + .375 (12)	
WEEK 55	17.0 + .208 (13)	16.6 + .257 (12)		18.1 + .617 (12)	
WEEK 56	16.2 + .326 (13)	15.1 + .259 (12)		18.0 + .550 (12)	
WEEK 57	17.9 + .196 (13)	17.1 + .235 (12)		19.4 + .282 (12)	*
WEEK 58	17.7 + .150 (12)†	16.5 + .190 (12)		18.7 + .424 (12)	
WEEK 59	17.2 + .177 (13)	17.0 + .216 (12)		18.4 + .368 (12)	
WEEK 60	17.5 + .146 (13)	16.7 + .190 (12)		18.9 + .405 (12)	*

ENTRIES ARE MEANS AND STANDARD ERRORS WITH N OF CAGES IN PARENTHESES
W = WILLIAMS TEST OF SIGNIFICANT CONTROL-TREATMENT DIFFERENCES
* CONFIDENCE LEVEL = .95
† ONE CAGE NOT INCLUDED IN AVERAGE BECAUSE OF WET FEED.

DEPENDENT VARIABLE	TREATMENT GROUPS: CONTROL	12.5 MG/KG	W	50 MG/KG	W
WEEK 61	18.2 + .125 (13)	17.2 + .253 (12)		19.2 + .356 (12)	
WEEK 62	17.6 + .142 (13)	16.6 + .252 (12)		19.9 + .588 (12)	*
WEEK 63	17.2 + .306 (13)	16.6 + .235 (12)		18.2 + .502 (12)	
WEEK 64	18.1 + .235 (13)	16.9 + .234 (12)		19.7 + .306 (12)	*
WEEK 65	17.4 + .260 (13)	16.5 + .275 (11)†		18.3 + .737 (12)	
WEEK 66	17.1 + .194 (13)	16.4 + .205 (12)		18.9 + .327 (12)	*
WEEK 67	16.3 + .277 (13)	16.1 + .144 (12)		18.9 + .307 (12)	*
WEEK 68	17.1 + .140 (13)	16.4 + .190 (12)		18.6 + .343 (12)	*
WEEK 69	17.4 + .153 (13)	16.9 + .132 (12)		18.7 + .336 (12)	*
WEEK 70	17.5 + .210 (13)	16.4 + .176 (12)		19.2 + .285 (12)	*
WEEK 71	17.9 + .095 (13)	16.8 + .193 (12)		18.0 + .377 (12)	
WEEK 72	17.4 + .134 (13)	16.4 + .213 (12)		18.4 + .485 (12)	

ENTRIES ARE MEANS AND STANDARD ERRORS WITH N OF CAGES IN PARENTHESES
W = WILLIAMS TEST OF SIGNIFICANT CONTROL-TREATMENT DIFFERENCES
* CONFIDENCE LEVEL = .95
† ONE CAGE NOT INCLUDED IN AVERAGE BECAUSE OF WET FEED.

DEPENDENT VARIABLE	TREATMENT GROUPS: CONTROL	12.5 MG/KG	W	50 MG/KG	W
WEEK 73	17.8 + .246 (13)	16.6 + .221 (12)		18.3 + .623 (12)	
WEEK 74	17.6 + .387 (13)	16.5 + .266 (12)		18.1 + .645 (12)	
WEEK 75	17.4 + .236 (13)	16.4 + .186 (12)		18.0 + .585 (12)	
WEEK 76	17.8 + .261 (13)	16.6 + .242 (12)		18.6 + .515 (12)	
WEEK 77	17.5 + .207 (12)	16.6 + .289 (12)		18.5 + .380 (12)	
WEEK 78	17.0 + .204 (13)	15.8 + .291 (12)		17.9 + .677 (12)	
WEEK 79	16.6 + .342 (13)	16.1 + .216 (12)		17.9 + .849 (12)	
WEEK 80	17.1 + .416 (13)	15.8 + .177 (12)		18.2 + .563 (11)	
WEEK 81	17.4 + .287 (13)	15.9 + .196 (12)		18.7 + .531 (11)	
WEEK 82	16.7 + .199 (13)	15.3 + .204 (12)		18.2 + .433 (11)	*
WEEK 83	17.0 + .246 (13)	15.9 + .220 (12)		19.5 + .688 (11)	*
WEEK 84	17.0 + .287 (13)	15.4 + .305 (12)		18.3 + .500 (10)†	

ENTRIES ARE MEANS AND STANDARD ERRORS WITH N OF CAGES IN PARENTHESES
W = WILLIAMS TEST OF SIGNIFICANT CONTROL-TREATMENT DIFFERENCES
* CONFIDENCE LEVEL = .95
† ONE CAGE NOT INCLUDED IN AVERAGE BECAUSE OF WET FEED.

APPENDIX D (CONTINUED)

DEPENDENT VARIABLE	TREATMENT GROUPS				
	CONTROL	12.5 MG/KG	W	50 MG/KG	W
WEEK 85	17.1 + .281 (13)	16.0 + .275 (12)		18.2 + .644 (11)	
WEEK 86	16.9 + .389 (13)	15.6 + .346 (12)		18.1 + .469 (11)	
WEEK 87	16.7 + .342 (13)	16.0 + .271 (12)		18.0 + .531 (10)	
WEEK 88	16.6 + .397 (13)	15.7 + .243 (12)		18.1 + .447 (11)	*
WEEK 89	16.4 + .620 (13)	15.9 + .212 (12)		17.1 + 1.01 (11)	
WEEK 90	16.6 + .332 (13)	15.4 + .248 (12)		16.8 + 1.18 (10)	
WEEK 91	17.2 + .368 (13)	17.2 + .248 (12)		18.3 + .330 (10)	
WEEK 92	17.4 + .231 (13)	16.8 + .274 (12)		19.1 + .390 (10)	*
WEEK 93	17.7 + .261 (13)	16.6 + .558 (12)		17.5 + .432 (10)	
WEEK 94	16.7 + .263 (13)	15.8 + .323 (12)		17.7 + .458 (9)†	
WEEK 95	16.8 + .408 (13)	16.1 + .369 (12)		17.8 + .479 (10)	
WEEK 96	16.9 + .266 (13)	15.9 + .371 (12)		17.7 + .509 (10)	

ENTRIES ARE MEANS AND STANDARD ERRORS WITH N OF CASES IN PARENTHESES
W = WILLIAMS TEST OF SIGNIFICANT CONTROL-TREATMENT DIFFERENCES
* CONFIDENCE LEVEL = .95
† ONE CAGE NOT INCLUDED IN AVERAGE BECAUSE OF WET FEED.

APPENDIX D (CONCLUDED)

DEPENDENT VARIABLE	TREATMENT GROUPS				
	CONTROL	12.5 MG/KG	W	50 MG/KG	W
WEEK 97	17.1 + .306 (13)	16.3 + .375 (12)		17.3 + .911 (10)	
WEEK 98	16.8 + .246 (13)	15.5 + .136 (12)		17.3 + .805 (9)	
WEEK 99	17.3 + .334 (13)	15.8 + .195 (12)		19.1 + .512 (9)	*
WEEK 100	16.7 + .351 (13)	15.8 + .286 (12)		18.5 + .642 (9)	
WEEK 101	17.2 + .420 (13)	16.2 + .400 (12)		17.9 + .661 (9)	
WEEK 102	15.5 + .228 (13)	14.5 + .424 (12)		17.1 + .522 (9)	
WEEK 103	16.4 + .347 (13)	15.5 + .326 (12)		19.3 + .792 (9)	*
WEEK 104	16.2 + .303 (13)	14.9 + .244 (12)		16.5 + .660 (9)	

ENTRIES ARE MEANS AND STANDARD ERRORS WITH N OF CAGES IN PARENTHESIS
W = WILLIAMS TEST OF SIGNIFICANT CONTROL-TREATMENT DIFFERENCES
* CONFIDENCE LEVEL = .95

APPENDIX E

AVERAGE WEEKLY FOOD CONSUMPTION (G/DAY) OF FEMALE RATS
TREATED WITH DAP

DEPENDENT VARIABLE	TREATMENT GROUPS					
	CONTROL	12.5 MG/KG	W	50 MG/KG	W	200 MG/KG	W
WEEK 1	8.4 + .389 (15)	9.3 + .109 (14)		8.3 + .146 (14)		4.5 + .161 (14)	*
WEEK 2	9.4 + .546 (15)	7.9 + .329 (14)		7.6 + .387 (14)		7.1 + .232 (14)	*
WEEK 3	10.7 + .214 (15)	10.8 + .224 (14)		10.1 + .152 (14)		7.4 + .066 (14)	*
WEEK 4	11.9 + .289 (15)	11.3 + .116 (14)		10.3 + .232 (14)	*	8.3 + .132 (14)	*
WEEK 5	12.2 + .259 (15)	12.0 + .214 (14)		10.0 + .128 (14)	*	8.2 + .186 (14)	*
WEEK 6	11.8 + .243 (15)	11.1 + .136 (14)		10.2 + .218 (14)	*	8.3 + .139 (14)	*
WEEK 7	11.7 + .187 (15)	11.0 + .185 (14)		9.7 + .160 (14)	*	8.6 + .131 (14)	*
WEEK 8	10.3 + .123 (15)	10.4 + .128 (14)		9.3 + .141 (14)	*	8.4 + .124 (14)	*
WEEK 9	11.5 + .128 (15)	10.7 + .177 (13)†		9.6 + .094 (14)		8.9 + .175 (14)	*
WEEK 10	10.7 + .099 (15)	10.7 + .157 (14)		9.4 + .161 (14)	*	8.9 + .220 (14)	*
WEEK 11	10.1 + .123 (15)	10.0 + .092 (14)		9.1 + .103 (14)		10.0 + .232 (14)	
WEEK 12	10.9 + .176 (15)	10.1 + .118 (14)		9.1 + .146 (14)	*	9.8 + .302 (14)	*

ENTRIES ARE MEANS AND STANDARD ERRORS WITH N OF CAGES IN PARENTHESES
W = WILLIAMS TEST OF SIGNIFICANT CONTROL-TREATMENT DIFFERENCES
* CONFIDENCE LEVEL = .95
† ONE CAGE NOT INCLUDED IN AVERAGE BECAUSE OF EXCESS BEDDING IN FEEDER CAUSING AN INACCURATE WEIGHT.

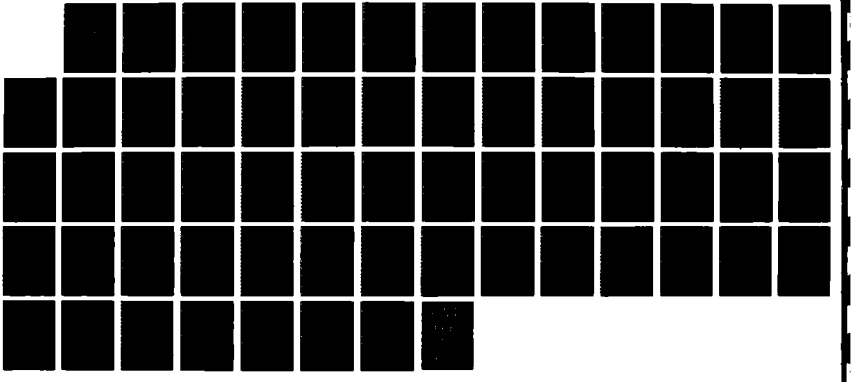
APPENDIX E (CONTINUED)

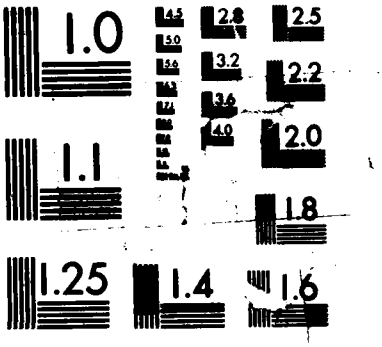
DEPENDENT VARIABLE	TREATMENT GROUPS			
	CONTROL	12.5 MG/KG W	50 MG/KG W	100 MG/KG † W
WEEK 13	10.4 + .121 (15)	9.7 + .184 (14)	9.3 + .083 (14)	11.2 + .177 (14)
WEEK 14	9 6 + .124 (15)	9.2 + .118 (14)	9.2 + .119 (14)	9.9 + .186 (14)
WEEK 15	11.9 + .266 (15)	10.3 + .176 (14) *	9.2 + .080 (14) *	10.7 + .171 (14) *
WEEK 16	10.7 + .122 (15)	10.3 + .128 (14)	9.3 + .120 (14)	11.3 + .204 (14)
WEEK 17	10.3 + .214 (15)	10.4 + .262 (14)	9.3 + .060 (14)	10.8 + .191 (14)
WEEK 18	10.8 + .183 (15)	10.0 + .153 (14)	9.3 + .139 (14)	10.6 + .295 (14)
WEEK 19	10.5 + .178 (15)	10.1 + .155 (14)	9.4 + .124 (14)	11.0 + .202 (14)
WEEK 20	10.8 + .207 (15)	10.0 + .115 (14)	9.2 + .158 (14)	10.7 + .189 (14)
WEEK 21	10.7 + .146 (15)	10.1 + .176 (14)	9.1 + .100 (14)	11.5 + .258 (14)
WEEK [illegible]	10.2 + .085 (15)	10.1 + .190 (14)	9.5 + .163 (14)	11.5 + .204 (14) *
[illegible]	9.9 + .186 (15)	9.6 + .249 (14)	9.0 + .126 (14)	11.2 + .274 (14) *
[illegible]	9.5 + .144 (15)	9.3 + .193 (14)	8.9 + .156 (12)†	11.9 + .171 (14) *

[illegible] AND STANDARD ERRORS WITH N OF CASES IN PARENTHESES
[illegible] SIGNIFICANT CONTROL-TREATMENT DIFFERENCES
[illegible] .95
[illegible] 100 MG/KG/DAY STARTING WITH WEEK 13.
[illegible] IN AVERAGE BECAUSE OF WEIGHING BALANCE MALFUNCTION.

AD-A187 273 CHRONIC MAMMALIAN TOXICOLOGICAL EFFECTS OF LAP WASTEWATER(U) SRI INTERNATIONAL MENLO PARK CA J M BROWN ET AL JUN 83 DAMD17-79-C-9121 3/3

UNCLASSIFIED F/G 24/4 NL





APPENDIX E (CONTINUED)

DEPENDENT VARIABLE	CONTROL	TREATMENT GROUPS					
		12.5 MG/KG	W	50 MG/KG	W	100 MG/KG†	W
WEEK 25	10.3 + .135 (15)	9.4 + .238 (14)		9.0 + .148 (14)		11.4 + .223 (14)	*
WEEK 26	10.5 + .259 (15)	10.3 + .183 (14)		8.6 + .126 (14)		11.6 + .170 (14)	
WEEK 27	11.9 + .204 (14)†	9.1 + .177 (14)	*	9.0 + .148 (14)	*	11.8 + .236 (14)	*
WEEK 28	8.6 + .214 (15)	9.1 + .191 (14)		8.8 + .190 (14)		12.3 + .233 (14)	*
WEEK 29	11.8 + .166 (15)	10.5 + .156 (14)		8.8 + .177 (14)		11.9 + .267 (14)	
WEEK 30	9.7 + .175 (15)	9.2 + .167 (14)		8.8 + .193 (14)		11.8 + .140 (13)§	*
WEEK 31	10.1 + .103 (15)	9.5 + .129 (14)		8.6 + .168 (14)		12.0 + .198 (14)	*
WEEK 32	9.9 + .195 (15)	9.4 + .089 (14)		8.5 + .155 (14)		11.7 + .246 (14)	*
WEEK 33	11.1 + .161 (15)	10.3 + .127 (14)		8.9 + .183 (14)		11.8 + .192 (13)	
WEEK 34	9.7 + .157 (15)	9.0 + .143 (14)		8.9 + .182 (14)			
WEEK 35	10.5 + .288 (15)	10.1 + .146 (14)		9.4 + .206 (14)			
WEEK 36	10.1 + .137 (15)	9.5 + .106 (14)		9.1 + .215 (14)	*		

ENTRIES ARE MEANS AND STANDARD ERRORS WITH N OF CAGES IN PARENTHESES
W = WILLIAMS TEST OF SIGNIFICANT CONTROL-TREATMENT DIFFERENCES
* CONFIDENCE LEVEL = .95
† HIGH DOSE TERMINATED AFTER 33 WEEKS ON TEST.
† ONE CAGE NOT INCLUDED IN AVERAGE BECAUSE OF INACCURATE FEEDER WEIGHT.
§ ONE CAGE NOT INCLUDED IN AVERAGE BECAUSE OF WET FEED.

APPENDIX E (CONTINUED)

DEPENDENT VARIABLE	CONTROL	TREATMENT GROUPS 12.5 MG/KG	W	50 MG/KG	W
WEEK 37	11.8 + .233 (15)	10.6 + .182 (14)		9.5 + .294 (14)	*
WEEK 38	10.4 + .153 (15)	9.4 + .089 (14)	*	9.4 + .286 (14)	
WEEK 39	10.6 + .210 (15)	9.9 + .124 (14)		9.9 + .213 (14)	
WEEK 40	10.4 + .135 (15)	9.8 + .068 (14)		9.9 + .222 (14)	
WEEK 41	10.5 + .264 (15)	9.9 + .171 (14)		10.3 + .214 (14)	
WEEK 42	9.9 + .154 (15)	9.4 + .106 (14)		9.7 + .187 (14)	
WEEK 43	10.6 + .077 (15)	9.9 + .109 (14)		9.8 + .188 (14)	*
WEEK 44	10.5 + .149 (15)	9.9 + .101 (14)		10.0 + .198 (14)	
WEEK 45	10.8 + .193 (15)	10.1 + .115 (14)		9.9 + .231 (14)	
WEEK 46	10.5 + .174 (15)	10.1 + .103 (14)		10.0 + .229 (14)	
WEEK 47	10.6 + .129 (15)	10.1 + .076 (14)		10.0 + .181 (14)	
WEEK 48	10.9 + .152 (15)	10.3 + .117 (14)		10.3 + .227 (14)	

ENTRIES ARE MEANS AND STANDARD ERRORS WITH N OF CASES IN PARENTHESES
W = WILLIAMS TEST OF SIGNIFICANT CONTROL-TREATMENT DIFFERENCES
* CONFIDENCE LEVEL = .95

APPENDIX E (CONTINUED)

DEPENDENT VARIABLE	CONTROL	TREATMENT GROUPS 12.5 MG/KG	W	50 MG/KG	W
WEEK 49	10.5 + .130 (15)	9.9 + .107 (14)		9.9 + .250 (14)	
WEEK 50	9.9 + .123 (15)	9.8 + .073 (14)		10.5 + .163 (14)	
WEEK 51	11.0 + .177 (15)	10.3 + .132 (14)		10.7 + .192 (14)	
WEEK 52	10.7 + .099 (15)	10.1 + .087 (14)		10.3 + .157 (14)	
WEEK 53	10.9 + .170 (13)	10.2 + .140 (12)		10.7 + .274 (12)	
WEEK 54	10.6 + .156 (13)	10.1 + .132 (12)		10.4 + .216 (12)	
WEEK 55	10.5 + .149 (13)	10.0 + .117 (12)		10.1 + .199 (12)	
WEEK 56	10.0 + .141 (13)	9.7 + .187 (12)		10.0 + .197 (12)	
WEEK 57	10.6 + .172 (13)	10.1 + .188 (12)		10.3 + .163 (12)	
WEEK 58	10.6 + .151 (13)	9.8 + .170 (12)		10.3 + .213 (12)	
WEEK 59	10.8 + .150 (13)	9.8 + .213 (12)		10.4 + .190 (12)	
WEEK 60	10.7 + .096 (13)	10.0 + .182 (12)		10.7 + .211 (12)	

ENTRIES ARE MEANS AND STANDARD ERRORS WITH N OF CAGES IN PARENTHESES
W = WILLIAMS TEST OF SIGNIFICANT CONTROL-TREATMENT DIFFERENCES
* CONFIDENCE LEVEL = .95

APPENDIX E (CONTINUED)

DEPENDENT VARIABLE	TREATMENT GROUPS: CONTROL	12.5 MG/KG	W	50 MG/KG	W
WEEK 61	11.9 + .116 (13)	10.4 + .129 (12)	*	10.6 + .184 (12)	*
WEEK 62	10.9 + .222 (13)	10.1 + .178 (12)		10.5 + .265 (12)	
WEEK 63	10.8 + .167 (13)	10.6 + .127 (12)		10.4 + .161 (12)	
WEEK 64	11.5 + .165 (13)	10.6 + .166 (12)		10.8 + .192 (12)	
WEEK 65	11.1 + .193 (13)	10.2 + .166 (12)		9.9 + .155 (12)	*
WEEK 66	10.4 + .166 (13)	10.0 + .153 (12)		10.2 + .322 (12)	
WEEK 67	10.8 + .144 (13)	10.5 + .144 (12)		10.5 + .223 (12)	
WEEK 68	10.3 + .288 (13)	10.4 + .145 (12)		10.3 + .301 (12)	
WEEK 69	11.2 + .167 (13)	10.7 + .147 (12)		10.9 + .234 (12)	
WEEK 70	10.9 + .177 (13)	10.4 + .158 (12)		10.1 + .270 (12)	
WEEK 71	11.4 + .170 (13)	10.5 + .170 (12)		10.7 + .227 (12)	
WEEK 72	10.9 + .158 (13)	10.3 + .112 (12)		10.2 + .201 (12)	

ENTRIES ARE MEANS AND STANDARD ERRORS WITH N OF CAGES IN PARENTHESES
W = WILLIAMS TEST OF SIGNIFICANT CONTROL-TREATMENT DIFFERENCES
* CONFIDENCE LEVEL = .95

APPENDIX E (CONTINUED)

DEPENDENT VARIABLE	TREATMENT GROUPS			
	CONTROL	12.5 MG/KG	W	50 MG/KG	W
WEEK 73	11.6 + .178 (13)	10.9 + .158 (12)		10.7 + .306 (12)	
WEEK 74	10.9 + .156 (13)	10.7 + .111 (12)		10.4 + .217 (12)	
WEEK 75	10.7 + .134 (13)	10.3 + .137 (12)		10.2 + .141 (12)	
WEEK 76	11.1 + .193 (13)	10.6 + .184 (12)		11.3 + .264 (12)	
WEEK 77	11.1 + .213 (13)	10.6 + .185 (12)		10.8 + .269 (12)	
WEEK 78	10.6 + .240 (13)	10.4 + .138 (12)		10.8 + .457 (12)	
WEEK 79	11.1 + .189 (13)	10.6 + .165 (12)		10.6 + .305 (12)	
WEEK 80	11.4 + .170 (13)	10.4 + .203 (12)		10.7 + .340 (11)	
WEEK 81	11.1 + .133 (13)	10.8 + .196 (12)		10.7 + .257 (12)	
WEEK 82	11.1 + .221 (13)	10.4 + .193 (12)		10.5 + .322 (12)	
WEEK 83	11.3 + .185 (13)	10.7 + .289 (12)		10.7 + .126 (12)	
WEEK 84	11.5 + .202 (13)	10.7 + .170 (12)		11.0 + .313 (12)	

ENTRIES ARE MEANS AND STANDARD ERRORS WITH N OF CAGES IN PARENTHESES
W = WILLIAMS TEST OF SIGNIFICANT CONTROL-TREATMENT DIFFERENCES
* CONFIDENCE LEVEL = .95

APPENDIX E (CONTINUED)

DEPENDENT VARIABLE	TREATMENT GROUPS				
	CONTROL	12.5 MG/KG	W	50 MG/KG	W
WEEK 85	11.3 + .170 (13)	10.5 + .135 (12)		10.5 + .221 (12)	
WEEK 86	10.9 + .174 (13)	10.4 + .121 (12)		10.6 + .207 (12)	
WEEK 87	11.4 + .212 (13)	11.1 + .110 (12)		10.9 + .272 (12)	
WEEK 88	11.0 + .218 (13)	10.3 + .135 (12)		10.9 + .257 (12)	
WEEK 89	11.2 + .238 (13)	9.7 + .167 (12)	*	10.3 + .264 (12)	
WEEK 90	10.4 + .228 (13)	9.1 + .150 (12)		10.4 + .288 (12)	
WEEK 91	11.5 + .209 (13)	10.9 + .154 (12)		11.6 + .299 (12)	
WEEK 92	11.5 + .262 (12)†	11.3 + .291 (12)		11.7 + .252 (12)	
WEEK 93	11.5 + .266 (13)	10.7 + .157 (12)		10.9 + .530 (12)	
WEEK 94	10.6 + .294 (13)	10.4 + .165 (12)		11.0 + .373 (11)†	
WEEK 95	10.9 + .315 (13)	10.5 + .269 (12)		11.2 + .330 (12)	
WEEK 96	11.1 + .365 (13)	10.5 + .182 (12)		11.3 + .340 (12)	

ENTRIES ARE MEANS AND STANDARD ERRORS WITH N OF CASES IN PARENTHESES
W = WILLIAMS TEST OF SIGNIFICANT CONTROL-TREATMENT DIFFERENCES
* CONFIDENCE LEVEL = .95
† ONE CAGE NOT INCLUDED IN AVERAGE BECAUSE FEEDER WAS FOUND EMPTY.

APPENDIX E (CONCLUDED)

DEPENDENT VARIABLE	TREATMENT GROUPS				
	CONTROL	12.5 MG/KG	W	50 MG/KG	W
WEEK 97	11.5 + .245 (13)	11.1 + .183 (12)		11.2 + .3[illegible] (12)	
WEEK 98	10.7 + .284 (13)	10.6 + .288 (12)		10.8 + .261 (12)	
WEEK 99	11.7 + .258 (13)	11.3 + .259 (12)		11.4 + .358 (12)	
WEEK 100	11.0 + .171 (13)	10.9 + .177 (12)		11.5 + .311 (11)	
WEEK 101	11.6 + .212 (13)	11.4 + .175 (12)		11.3 + .311 (12)	
WEEK 102	9.9 + .243 (13)	10.6 + .214 (12)		11.4 + .272 (12)	*
WEEK 103	11.4 + .284 (13)	11.1 + .205 (12)		10.7 + .327 (12)	
WEEK 104	10.7 + .314 (13)	10.2 + .193 (12)		10.7 + .261 (12)	

ENTRIES ARE MEANS AND STANDARD ERRORS WITH N OF CAGES IN PARENTHESIS
W = WILLIAMS TEST OF SIGNIFICANT CONTROL-TREATMENT DIFFERENCES
* CONFIDENCE LEVEL = .95

APPENDIX F

AVERAGE WEEKLY FOOD CONSUMPTION (G/KG BODY WEIGHT/DAY)
OF MALE RATS TREATED WITH MAP

DEPENDENT VARIABLE	TREATMENT GROUPS					
	CONTROL	12.5 MG/KG	W	50 MG/KG	W	200 MG/KG	W
WEEK 1	85.7 + .686 (15)	85.5 + .895 (14)		80.6 + 1.00 (14)		51.3 + 1.21 (14)	*
WEEK 2	75.9 + .564 (15)	73.2 + 1.25 (14)		73.1 + 1.54 (14)		79.9 + 1.58 (14)	
WEEK 3	74.8 + .506 (15)	76.7 + .808 (14)		75.8 + .835 (14)		75.2 + .657 (14)	
WEEK 4	76.6 + 1.58 (15)	73.2 + 1.24 (14)		76.2 + 1.80 (14)		79.1 + 1.52 (14)	
WEEK 5	72.5 + .979 (15)	70.0 + .862 (14)		67.3 + .995 (14)		69.4 + 1.45 (14)	
WEEK 6	68.4 + .978 (15)	65.6 + .737 (14)		65.7 + .835 (14)		68.5 + 1.41 (14)	
WEEK 7	65.3 + .962 (15)	63.3 + .873 (14)		62.7 + .799 (14)		71.0 + 2.85 (14)	
WEEK 8	57.2 + .534 (15)	59.1 + .560 (14)		58.3 + 1.54 (14)		68.1 + 2.23 (14)	*
WEEK 9	55.8 + .547 (15)	56.0 + .757 (14)		54.5 + .870 (14)		63.3 + 1.63 (13)	*
WEEK 10	54.6 + .638 (15)	54.2 + .583 (14)		52.6 + .893 (14)		59.5 + 1.70 (14)	
WEEK 11	51.4 + .481 (15)	50.8 + .483 (14)		50.3 + .672 (14)		62.0 + 2.09 (14)	*
WEEK 12	52.0 + .372 (15)	51.1 + .590 (14)		49.9 + 1.00 (14)		62.0 + 1.93 (14)	*

ENTRIES ARE MEANS AND STANDARD ERRORS WITH N OF CAGES IN PARENTHESES
W = WILLIAMS TEST OF SIGNIFICANT CONTROL-TREATMENT DIFFERENCES
* CONFIDENCE LEVEL = .95

APPENDIX F (CONTINUED)

DEPENDENT VARIABLE	CONTROL	TREATMENT GROUPS 12.5 MG/KG	W	50 MG/KG	W	100 MG/KG	W
WEEK 13	48.8 + .347 (15)	48.6 + .438 (14)		48.3 + .648 (14)		65.4 + 1.39 (14)	*
WEEK 14	48.8 + .572 (15)	46.1 + .333 (14)		46.8 + .472 (14)		62.4 + 1.80 (14)	*
WEEK 15	50.6 + .437 (15)	47.7 + .448 (14)		48.2 + .976 (14)		59.0 + 1.45 (14)	*
WEEK 16	50.2 + .370 (15)	48.4 + .365 (14)		47.1 + .723 (14)		64.8 + 1.53 (14)	*
WEEK 17	49.0 + .371 (15)	48.2 + .712 (14)		48.1 + .934 (14)		65.5 + 1.14 (14)	*
WEEK 18	46.4 + .514 (15)	46.5 + .442 (14)		47.6 + .742 (14)		61.9 + 1.16 (14)	*
WEEK 19	47.0 + .423 (15)	46.7 + .592 (14)		48.9 + .913 (14)		61.7 + .929 (14)	*
WEEK 20	46.9 + .415 (15)	45.6 + .424 (14)		48.9 + 1.01 (14)		59.3 + 1.09 (14)	*
WEEK 21	47.9 + .366 (15)	46.9 + .546 (14)		51.8 + 1.32 (14)		64.0 + 1.26 (14)	*
WEEK 22	46.3 + .584 (15)	45.6 + .640 (14)		51.9 + 1.26 (14)		62.9 + 1.86 (14)	*
WEEK 23	44.1 + .800 (15)	44.6 + 1.02 (14)		49.8 + 1.14 (14)		60.6 + 2.04 (14)	*
WEEK 24	45.8 + .546 (15)	46.3 + .765 (14)		54.5 + 1.44 (14)	*	58.4 + 2.17 (14)	*

ENTRIES ARE MEANS AND STANDARD ERRORS WITH N OF CASES IN PARENTHESES
W = WILLIAMS TEST OF SIGNIFICANT CONTROL-TREATMENT DIFFERENCES
* CONFIDENCE LEVEL = .95
DOSE LEVEL REDUCED TO 100 MG/KG/DAY STARTING WITH WEEK 13.

DEPENDENT VARIABLE	CONTROL	TREATMENT GROUPS 12.5 MG/KG	W	50 MG/KG	W	100 MG/KG †	W
WEEK 25	46.9 + .576 (15)	44.8 + .965 (14)		52.3 + 1.38 (14)		59.3 + 2.32 (14)	*
WEEK 26	45.9 + .672 (15)	44.5 + .602 (14)		53.2 + 1.31 (14)	*	62.4 + 2.97 (12)	*
WEEK 27	45.5 + .762 (15)	43.5 + .680 (14)		53.7 + 1.24 (14)	*	57.2 + 1.76 (13)	*
WEEK 28	41.2 + .475 (15)	40.5 + .616 (14)		51.2 + 1.20 (14)	*	58.7 + 2.71 (13)	*
WEEK 29	44.3 + .513 (15)	44.4 + .380 (14)		48.9 + 1.18 (14)		60.4 + 2.42 (13)	*
WEEK 30	41.5 + .383 (15)	40.6 + .469 (14)		49.1 + .900 (14)	*	55.0 + 1.46 (13)	*
WEEK 31	40.8 + .319 (15)	40.9 + .591 (14)		49.7 + 1.11 (14)	*	55.8 + 2.42 (13)	*
WEEK 32	40.4 + .598 (15)	40.0 + .333 (14)		47.2 + .905 (14)	*	48.1 + 3.50 (13)	*
WEEK 33	43.2 + .538 (15)	42.5 + .467 (14)		49.9 + 1.03 (14)	*	53.1 + 2.45 (12)	*
WEEK 34	40.5 + .542 (15)	38.9 + .464 (14)		46.9 + 1.21 (14)	*		
WEEK 35	41.1 + .430 (15)	40.2 + .606 (14)		48.9 + 1.03 (14)	*		
WEEK 36	40.4 + .443 (15)	39.3 + .462 (14)		47.8 + 1.10 (14)	*		

ENTRIES ARE MEANS AND STANDARD ERRORS WITH N OF CAGES IN PARENTHESES
W = WILLIAMS TEST OF SIGNIFICANT CONTROL-TREATMENT DIFFERENCES
* CONFIDENCE LEVEL = .95
† HIGH DOSE TERMINATED AFTER 33 WEEKS ON TEST.

APPENDIX F (CONTINUED)

DEPENDENT VARIABLE	TREATMENT GROUPS: CONTROL	12.5 MG/KG	W	50 MG/KG	W
WEEK 37	43.4 + .390 (15)	42.5 + .516 (14)		50.9 + 1.15 (14)	*
WEEK 38	39.7 + .605 (15)	38.5 + .440 (14)		48.4 + .803 (14)	*
WEEK 39	40.0 + .515 (15)	39.9 + .372 (14)		54.9 + 1.28 (14)	*
WEEK 40	40.2 + .424 (15)	39.3 + .520 (14)		54.6 + 1.04 (14)	*
WEEK 41	39.4 + .406 (15)	39.2 + .443 (14)		52.7 + 1.26 (14)	*
WEEK 42	38.2 + .390 (15)	37.8 + .400 (14)		52.9 + 1.08 (14)	*
WEEK 43	38.9 + .611 (15)	39.1 + .403 (14)		54.2 + .838 (14)	*
WEEK 44	38.4 + .410 (15)	38.7 + .370 (14)		51.8 + 1.00 (14)	*
WEEK 45	39.5 + .460 (15)	39.2 + .382 (14)		52.7 + .827 (14)	*
WEEK 46	39.2 + .550 (15)	38.4 + .496 (14)		49.0 + .830 (13)	*
WEEK 47	39.4 + .462 (15)	38.4 + .533 (14)		49.7 + .730 (14)	*
WEEK 48	39.1 + .389 (15)	38.8 + .453 (14)		49.3 + .790 (14)	*

ENTRIES ARE MEANS AND STANDARD ERRORS WITH N OF CASES IN PARENTHESES
W = WILLIAMS TEST OF SIGNIFICANT CONTROL-TREATMENT DIFFERENCES
* CONFIDENCE LEVEL = .95

APPENDIX F (CONTINUED)

DEPENDENT VARIABLE	CONTROL	TREATMENT GROUPS 12.5 MG/KG	W	50 MG/KG	W
WEEK 49	38.1 + .426 (15)	38.4 + .441 (14)		50.0 + .897 (14)	*
WEEK 50	37.6 + .388 (15)	37.1 + .573 (14)		48.7 + .727 (14)	*
WEEK 51	38.6 + .428 (15)	38.8 + .325 (14)		51.5 + .908 (14)	*
WEEK 52	38.4 + .486 (15)	37.9 + .432 (14)		52.5 + 1.08 (14)	*
WEEK 53	37.4 + .517 (13)	37.5 + .361 (12)		47.4 + .740 (12)	*
WEEK 54	37.9 + .487 (13)	37.3 + .491 (12)		47.5 + .926 (12)	*
WEEK 55	36.4 + .550 (13)	36.6 + .560 (12)		46.4 + 1.27 (12)	*
WEEK 56	34.9 + .723 (13)	33.6 + .566 (12)		46.3 + 1.13 (12)	*
WEEK 57	38.3 + .493 (13)	37.7 + .492 (12)		49.3 + .494 (12)	*
WEEK 58	37.8 + .387 (12)	36.4 + .413 (12)		47.4 + 1.00 (12)	*
WEEK 59	36.5 + .401 (13)	37.1 + .449 (12)		46.5 + .826 (12)	*
WEEK 60	37.1 + .389 (13)	36.4 + .347 (12)		47.6 + .929 (12)	*

ENTRIES ARE MEANS AND STANDARD ERRORS WITH N OF CAGES IN PARENTHESES
W = WILLIAMS TEST OF SIGNIFICANT CONTROL-TREATMENT DIFFERENCES
* CONFIDENCE LEVEL = .95

APPENDIX F (CONTINUED)

DEPENDENT VARIABLE	TREATMENT GROUPS					
	CONTROL	12.5 MG/KG	W	50 MG/KG	W	
WEEK 61	38.2 + .382 (13)	37.4 + .501 (12)		48.5 + .849 (12)	*	
WEEK 62	37.0 + .396 (13)	36.0 + .489 (12)		50.3 + 1.17 (12)	*	
WEEK 63	35.9 + .677 (13)	35.8 + .480 (12)		46.0 + 1.21 (12)	*	
WEEK 64	37.7 + .566 (13)	36.4 + .461 (12)		49.9 + .665 (12)	*	
WEEK 65	36.4 + .560 (13)	35.7 + .410 (11)		46.3 + 1.65 (12)	*	
WEEK 66	35.4 + .517 (13)	35.3 + .453 (12)		47.5 + .488 (12)	*	
WEEK 67	34.0 + .627 (13)	34.7 + .359 (12)		47.6 + .623 (12)	*	
WEEK 68	35.9 + .348 (13)	35.4 + .398 (12)		46.8 + .824 (12)	*	
WEEK 69	36.4 + .360 (13)	36.4 + .381 (12)		46.6 + .796 (12)	*	
WEEK 70	36.5 + .446 (13)	35.5 + .413 (12)		47.7 + .857 (12)	*	
WEEK 71	37.1 + .236 (13)	36.0 + .366 (12)		44.8 + .784 (12)	*	
WEEK 72	36.0 + .365 (13)	35.4 + .409 (12)		45.6 + 1.26 (12)	*	

ENTRIES ARE MEANS AND STANDARD ERRORS WITH N OF CAGES IN PARENTHESES
W = WILLIAMS TEST OF SIGNIFICANT CONTROL-TREATMENT DIFFERENCES
* CONFIDENCE LEVEL = .95

APPENDIX F (CONTINUED)

DEPENDENT VARIABLE	TREATMENT GROUPS			
	CONTROL	12.5 MG/KG	W	50 MG/KG	W
WEEK 73	36.8 + .563 (13)	35.6 + .432 (12)		45.5 + 1.80 (12)	*
WEEK 74	36.4 + .714 (13)	35.5 + .535 (12)		45.0 + 1.60 (12)	*
WEEK 75	35.8 + .459 (13)	35.3 + .459 (12)		44.4 + 1.46 (12)	*
WEEK 76	36.7 + .552 (13)	35.8 + .614 (12)		46.0 + 1.28 (12)	*
WEEK 77	36.2 + .344 (12)	35.8 + .637 (12)		45.6 + .921 (12)	*
WEEK 78	35.1 + .421 (13)	33.9 + .679 (12)		43.7 + 1.78 (12)	*
WEEK 79	34.3 + .682 (13)	34.7 + .482 (12)		44.1 + 2.10 (12)	*
WEEK 80	35.3 + .766 (13)	34.1 + .413 (12)		44.4 + 1.27 (11)	*
WEEK 81	35.7 + .658 (13)	34.3 + .437 (12)		45.8 + 1.22 (11)	*
WEEK 82	34.4 + .410 (13)	33.2 + .355 (12)		44.7 + 1.04 (11)	*
WEEK 83	35.0 + .436 (13)	34.2 + .430 (12)		47.7 + 1.54 (11)	*
WEEK 84	35.2 + .594 (13)	33.3 + .477 (12)		44.8 + 1.42 (10)	*

ENTRIES ARE MEANS AND STANDARD ERRORS WITH N OF CAGES IN PARENTHESES
W = WILLIAMS TEST OF SIGNIFICANT CONTROL-TREATMENT DIFFERENCES
* CONFIDENCE LEVEL = .95

APPENDIX F (CONTINUED)

DEPENDENT VARIABLE	TREATMENT GROUPS				
	CONTROL	12.5 MG/KG	W	50 MG/KG	W
WEEK 85	35.3 + .459 (13)	34.6 + .478 (12)		44.9 + 1.37 (11)	*
WEEK 86	34.8 + .721 (13)	34.1 + .661 (12)		44.7 + 1.22 (11)	*
WEEK 87	34.5 + .604 (13)	34.7 + .508 (12)		44.4 + 1.60 (10)	*
WEEK 88	34.4 + .634 (13)	34.2 + .440 (12)		44.5 + 1.24 (11)	*
WEEK 89	34.4 + .945 (13)	34.9 + .362 (12)		41.9 + 3.43 (11)	*
WEEK 90	34.6 + .547 (13)	33.9 + .470 (12)		41.9 + 3.05 (10)	*
WEEK 91	35.8 + .697 (13)	37.7 + .437 (12)		45.6 + 1.14 (10)	*
WEEK 92	36.6 + .439 (13)	37.3 + .425 (12)		48.4 + 1.20 (10)	*
WEEK 93	36.8 + .544 (13)	36.5 + 1.01 (12)		43.7 + 1.23 (10)	*
WEEK 94	34.8 + .389 (13)	34.9 + .573 (12)		43.9 + 1.46 (9)	*
WEEK 95	35.1 + .723 (13)	35.7 + .691 (12)		44.5 + 1.28 (10)	*
WEEK 96	35.2 + .486 (13)	35.2 + .651 (12)		44.4 + 1.47 (10)	*

ENTRIES ARE MEANS AND STANDARD ERRORS WITH N OF CASES IN PARENTHESES
W = WILLIAMS TEST OF SIGNIFICANT CONTROL-TREATMENT DIFFERENCES
* CONFIDENCE LEVEL = .95

APPENDIX F (CONCLUDED)

DEPENDENT VARIABLE	TREATMENT GROUPS				
	CONTROL	12.5 MG/KG	W	50 MG/KG	W
WEEK 97	35.9 + .624 (13)	36.1 + .771 (12)		44.0 + 2.38 (10)	*
WEEK 98	35.1 + .527 (13)	34.4 + .405 (12)		44.0 + 2.02 (9)	*
WEEK 99	36.6 + .624 (13)	35.6 + .548 (12)		49.0 + 1.54 (9)	*
WEEK 100	35.4 + .660 (13)	35.9 + .685 (12)		47.7 + 1.57 (9)	*
WEEK 101	36.5 + .818 (13)	36.8 + .840 (12)		46.4 + 1.81 (9)	*
WEEK 102	33.3 + .382 (13)	33.2 + .887 (12)		45.3 + 1.31 (9)	*
WEEK 103	35.4 + .472 (13)	35.8 + .697 (12)		51.4 + 2.06 (9)	*
WEEK 104	35.2 + .560 (13)	34.5 + .564 (12)		45.1 + 2.32 (9)	*

ENTRIES ARE MEANS AND STANDARD ERRORS WITH N OF CAGES IN PARENTHESIS
W = WILLIAMS TEST OF SIGNIFICANT CONTROL-TREATMENT DIFFERENCES
* CONFIDENCE LEVEL = .95

APPENDIX G

AVERAGE WEEKLY FOOD CONSUMPTION (G/KG BODY WEIGHT/DAY)
OF FEMALE RATS TREATED WITH MAP

DEPENDENT VARIABLE	TREATMENT GROUPS					
	CONTROL	12.5 MG/KG	W	50 MG/KG	W	200 MG/KG	W
WEEK 1	79.3 + 2.44 (15)	85.2 + .737 (14)		80.1 + 1.29 (14)		52.5 + 1.61 (14)	*
WEEK 2	77.6 + 3.79 (15)	67.4 + 1.86 (14)		68.0 + 2.49 (14)		76.0 + 1.75 (14)	
WEEK 3	80.2 + 2.16 (15)	82.2 + 1.59 (14)		80.5 + 1.27 (14)		72.6 + .877 (14)	
WEEK 4	82.7 + 1.98 (15)	80.0 + 1.02 (14)		77.9 + 1.89 (14)		75.2 + 1.12 (14)	
WEEK 5	80.1 + 1.51 (15)	80.6 + 1.27 (14)		71.8 + .744 (14)	*	70.0 + 1.27 (14)	*
WEEK 6	74.5 + 1.48 (15)	71.9 + 1.02 (14)		70.5 + 1.44 (14)		67.2 + .899 (14)	*
WEEK 7	72.2 + 1.27 (15)	68.6 + 1.25 (14)		64.8 + 1.06 (14)	*	66.2 + .831 (14)	*
WEEK 8	61.2 + .535 (15)	63.3 + .779 (14)		61.1 + .949 (14)		62.5 + .731 (14)	
WEEK 9	66.1 + .798 (15)	59.2 + 4.64 (14)		62.2 + .603 (14)		63.7 + 1.10 (14)	
WEEK 10	60.1 + .676 (15)	61.9 + .848 (14)		59.1 + 1.08 (14)		60.4 + 1.24 (14)	
WEEK 11	55.9 + .695 (15)	57.6 + .543 (14)		56.6 + .617 (14)		65.3 + 1.38 (14)	*
WEEK 12	59.4 + .953 (15)	57.4 + .738 (14)		55.7 + .876 (14)		61.9 + 1.46 (14)	

ENTRIES ARE MEANS AND STANDARD ERRORS WITH N OF CAGES IN PARENTHESES
W = WILLIAMS TEST OF SIGNIFICANT CONTROL-TREATMENT DIFFERENCES
* CONFIDENCE LEVEL = .95

APPENDIX G (CONTINUED)

DEPENDENT VARIABLE	CONTROL	TREATMENT GROUPS					
		12.5 MG/KG	W	50 MG/KG	W	100 MG/KG †	W
WEEK 13	55.7 + .643 (15)	54.5 + 1.00 (14)		55.8 + .564 (14)		66.9 + .732 (14)	*
WEEK 14	50.8 + .487 (15)	51.0 + .599 (14)		54.4 + .580 (14)	*	57.7 + .534 (14)	*
WEEK 15	62.4 + 1.45 (15)	56.2 + .989 (14)	*	54.7 + .553 (14)	*	59.6 + .544 (14)	*
WEEK 16	55.5 + .606 (15)	54.9 + 1.15 (14)		54.3 + .548 (14)		62.0 + .659 (14)	*
WEEK 17	53.0 + 1.03 (15)	55.0 + 1.84 (14)		53.6 + .381 (14)		58.0 + .707 (14)	
WEEK 18	54.9 + .898 (15)	54.0 + .751 (14)		53.6 + .609 (14)		55.7 + 1.17 (14)	
WEEK 19	52.8 + .761 (15)	53.4 + .813 (14)		53.5 + .510 (14)		56.8 + .514 (14)	*
WEEK 20	53.8 + .976 (15)	52.0 + .631 (14)		51.8 + .811 (14)		53.4 + .547 (14)	
WEEK 21	52.8 + .542 (15)	52.1 + .877 (14)		51.5 + .343 (14)		56.7 + .984 (14)	
WEEK 22	50.2 + .450 (15)	52.0 + 1.00 (14)		53.2 + .749 (14)		55.5 + .747 (14)	*
WEEK 23	48.8 + .736 (15)	49.7 + 1.29 (14)		50.2 + .471 (14)		53.6 + .923 (14)	
WEEK 24	47.0 + .633 (15)	47.7 + .894 (14)		49.0 + .634 (12)		55.8 + .637 (14)	*

ENTRIES ARE MEANS AND STANDARD ERRORS WITH N OF CASES IN PARENTHESES
W = WILLIAMS TEST OF SIGNIFICANT CONTROL-TREATMENT DIFFERENCES
* CONFIDENCE LEVEL = .95
† DOSE LEVEL REDUCED TO 100 MG/KG/DAY STARTING WITH WEEK 13.

APPENDIX G (CONTINUED)

DEPENDENT VARIABLE	CONTROL	TREATMENT GROUPS					
		12.5 MG/KG	W	50 MG/KG	W	100 MG/KG†	W
WEEK 25	50.2 ± .620 (15)	48.6 ± 1.03 (14)		49.7 ± .530 (14)		52.7 ± .742 (14)	
WEEK 26	51.2 ± 1.30 (15)	52.6 ± 1.02 (14)		47.2 ± .549 (14)		52.9 ± .590 (14)	
WEEK 27	57.7 ± .795 (14)	46.3 ± .801 (14)	*	48.8 ± .599 (14)	*	53.5 ± .587 (14)	*
WEEK 28	41.2 ± .923 (15)	45.9 ± .975 (14)	*	47.5 ± .852 (14)	*	54.6 ± .792 (14)	*
WEEK 29	56.1 ± .850 (15)	52.4 ± .780 (14)		47.2 ± .750 (14)	*	52.3 ± .854 (14)	*
WEEK 30	45.6 ± .648 (15)	45.8 ± .771 (14)		46.4 ± .742 (14)		51.6 ± .350 (13)	*
WEEK 31	47.2 ± .517 (15)	46.7 ± .603 (14)		45.4 ± .544 (14)		52.5 ± .572 (14)	*
WEEK 32	46.2 ± .715 (15)	46.4 ± .412 (14)		45.1 ± .454 (14)		50.8 ± .684 (14)	*
WEEK 33	51.4 ± .768 (15)	50.4 ± .618 (14)		47.0 ± .462 (14)		50.8 ± .641 (13)	
WEEK 34	44.1 ± .653 (15)	43.7 ± .646 (14)		46.1 ± .488 (14)			
WEEK 35	47.5 ± 1.20 (15)	48.3 ± .666 (14)		48.1 ± .558 (14)			
WEEK 36	45.3 ± .559 (15)	45.4 ± .483 (14)		46.4 ± .550 (14)			

ENTRIES ARE MEANS AND STANDARD ERRORS WITH N OF CAGES IN PARENTHESES
W = WILLIAMS TEST OF SIGNIFICANT CONTROL-TREATMENT DIFFERENCES
* CONFIDENCE LEVEL = .95
† HIGH DOSE TERMINATED AFTER 33 WEEKS ON TEST.

APPENDIX G (CONTINUED)

DEPENDENT VARIABLE	TREATMENT GROUPS					
	CONTROL	12.5 MG/KG	W	50 MG/KG	W	
WEEK 37	52.4 ± .919 (15)	50.9 ± .845 (14)		48.1 ± 1.02 (14)		
WEEK 38	45.7 ± .510 (15)	44.2 ± .405 (14)		47.0 ± .951 (14)		
WEEK 39	46.5 ± .734 (15)	46.4 ± .477 (14)		49.0 ± .588 (14)		
WEEK 40	45.7 ± .546 (15)	46.3 ± .370 (14)		49.0 ± .583 (14)		*
WEEK 41	45.3 ± .930 (15)	46.2 ± .736 (14)		50.5 ± .822 (14)		*
WEEK 42	42.8 ± .707 (15)	43.9 ± .615 (14)		47.3 ± .509 (14)		*
WEEK 43	45.7 ± .275 (15)	46.3 ± .438 (14)		47.9 ± .755 (14)		
WEEK 44	44.9 ± .489 (15)	45.8 ± .321 (14)		47.9 ± .579 (14)		*
WEEK 45	45.8 ± .733 (15)	46.4 ± .446 (14)		47.0 ± .613 (14)		
WEEK 46	44.3 ± .650 (15)	46.4 ± .577 (14)		47.3 ± .757 (14)		
WEEK 47	44.3 ± .497 (15)	46.1 ± .307 (14)		47.4 ± .493 (14)		*
WEEK 48	45.4 ± .445 (15)	47.0 ± .543 (14)		48.6 ± .658 (14)		*

ENTRIES ARE MEANS AND STANDARD ERRORS WITH N OF CASES IN PARENTHESES
W = WILLIAMS TEST OF SIGNIFICANT CONTROL-TREATMENT DIFFERENCES
* CONFIDENCE LEVEL = .95

APPENDIX G (CONTINUED)

DEPENDENT VARIABLE	TREATMENT GROUPS				
	CONTROL	12.5 MG/KG	W	50 MG/KG	W
WEEK 49	43.9 ± .434 (15)	45.2 ± .374 (14)		47.1 ± .521 (14)	*
WEEK 50	41.1 ± .328 (15)	44.1 ± .362 (14)	*	48.5 ± .625 (14)	*
WEEK 51	44.9 ± .595 (15)	46.4 ± .585 (14)		49.1 ± .554 (14)	*
WEEK 52	44.0 ± .414 (15)	45.5 ± .251 (14)		47.2 ± .712 (14)	*
WEEK 53	44.0 ± .393 (13)	45.1 ± .462 (12)		47.4 ± .904 (12)	*
WEEK 54	42.6 ± .411 (13)	44.6 ± .400 (12)		46.6 ± .776 (12)	*
WEEK 55	41.8 ± .306 (13)	43.7 ± .430 (12)		44.6 ± .433 (12)	*
WEEK 56	39.7 ± .507 (13)	42.8 ± .725 (12)		44.2 ± .732 (12)	*
WEEK 57	41.8 ± .489 (13)	44.3 ± .562 (12)		45.4 ± .556 (12)	*
WEEK 58	41.8 ± .563 (13)	43.0 ± .442 (12)		45.4 ± .607 (12)	*
WEEK 59	42.0 ± .379 (13)	42.6 ± .638 (12)		45.0 ± .408 (12)	*
WEEK 60	41.4 ± .489 (13)	43.5 ± .433 (12)		46.3 ± .651 (12)	*

ENTRIES ARE MEANS AND STANDARD ERRORS WITH N OF CAGES IN PARENTHESES
W = WILLIAMS TEST OF SIGNIFICANT CONTROL-TREATMENT DIFFERENCES
* CONFIDENCE LEVEL = .95

APPENDIX G (CONTINUED)

DEPENDENT VARIABLE	TREATMENT GROUPS				
	CONTROL	12.5 MG/KG	W	50 MG/KG	W
WEEK 61	45.0 + .375 (13)	44.4 + .373 (12)		45.4 + .705 (12)	
WEEK 62	40.9 + .664 (13)	43.3 + .734 (12)		44.4 + .941 (12)	
WEEK 63	40.2 + .544 (13)	44.4 + .485 (12)	*	43.9 + .667 (12)	*
WEEK 64	42.4 + .624 (13)	44.4 + .519 (12)		45.1 + .564 (12)	
WEEK 65	40.5 + .393 (13)	42.5 + .591 (12)		41.9 + .720 (12)	
WEEK 66	37.7 + .566 (13)	41.3 + .562 (12)		42.8 + 1.06 (12)	*
WEEK 67	38.9 + .367 (13)	42.7 + .417 (12)	*	44.1 + 1.10 (12)	*
WEEK 68	37.5 + .811 (13)	42.5 + .587 (12)	*	42.8 + 1.13 (12)	*
WEEK 69	39.8 + .373 (13)	43.1 + .617 (12)		44.6 + 1.10 (12)	*
WEEK 70	38.7 + .341 (13)	42.0 + .573 (12)		40.6 + 1.22 (12)	
WEEK 71	39.9 + .434 (13)	41.9 + .675 (12)		43.0 + 1.07 (12)	
WEEK 72	37.9 + .455 (13)	40.5 + .348 (12)		41.5 + .701 (12)	*

ENTRIES ARE MEANS AND STANDARD ERRORS WITH N OF CAGES IN PARENTHESES
W = WILLIAMS TEST OF SIGNIFICANT CONTROL-TREATMENT DIFFERENCES
* CONFIDENCE LEVEL = .95

APPENDIX G (CONTINUED)

DEPENDENT VARIABLE	TREATMENT GROUPS: CONTROL	12.5 MG/KG	W	50 MG/KG	W
WEEK 73	40.1 + .600 (13)	42.9 + .716 (12)		43.4 + 1.02 (12)	
WEEK 74	37.7 + .582 (13)	41.6 + .446 (12)	*	41.9 + .732 (12)	*
WEEK 75	36.6 + .329 (13)	39.9 + .404 (12)	*	41.5 + .593 (12)	*
WEEK 76	37.9 + .612 (13)	41.0 + .668 (12)		45.3 + .979 (12)	*
WEEK 77	37.6 + .496 (13)	41.1 + .509 (12)		43.2 + .985 (12)	*
WEEK 78	35.6 + .608 (13)	39.8 + .365 (12)		42.9 + 1.71 (12)	*
WEEK 79	37.4 + .406 (13)	40.4 + .293 (12)		42.5 + .947 (12)	*
WEEK 80	38.1 + .626 (13)	39.2 + .427 (12)		42.4 + 1.02 (11)	*
WEEK 81	36.8 + .563 (13)	40.8 + .605 (12)	*	42.0 + .903 (12)	*
WEEK 82	36.5 + .638 (13)	38.9 + .661 (12)		41.3 + .924 (12)	*
WEEK 83	37.1 + .359 (13)	39.8 + .796 (12)		41.9 + .530 (12)	*
WEEK 84	37.4 + .477 (13)	39.7 + .458 (12)		43.5 + 1.01 (12)	*

ENTRIES ARE MEANS AND STANDARD ERRORS WITH N OF CAGES IN PARENTHESES
W = WILLIAMS TEST OF SIGNIFICANT CONTROL-TREATMENT DIFFERENCES
* CONFIDENCE LEVEL = .95

APPENDIX G (CONTINUED)

DEPENDENT VARIABLE	TREATMENT GROUPS: CONTROL	12.5 MG/KG	W	50 MG/KG	W
WEEK 85	36.7 + .325 (13)	38.6 + .421 (12)		41.0 + .701 (12)	*
WEEK 86	35.4 + .556 (13)	38.2 + .400 (12)		41.9 + .832 (12)	*
WEEK 87	36.9 + .470 (13)	40.6 + .492 (12)	*	42.9 + .864 (12)	*
WEEK 88	35.5 + .539 (13)	37.4 + .364 (12)		42.5 + 1.10 (12)	*
WEEK 89	36.1 + .460 (13)	36.0 + .679 (12)		40.5 + .947 (12)	*
WEEK 90	33.6 + .509 (13)	33.8 + .474 (12)		40.6 + .950 (12)	*
WEEK 91	36.9 + .299 (13)	40.2 + .455 (12)	*	45.3 + .845 (12)	*
WEEK 92	37.3 + .655 (12)	41.7 + 1.26 (12)		45.2 + .915 (12)	*
WEEK 93	36.8 + .522 (13)	39.0 + .787 (12)		42.0 + 1.88 (12)	
WEEK 94	34.2 + .568 (13)	37.8 + .615 (12)		42.4 + 1.12 (11)	*
WEEK 95	34.9 + .710 (13)	38.4 + .750 (12)		43.5 + 1.45 (12)	*
WEEK 96	35.5 + .955 (13)	37.5 + .510 (12)		43.3 + .993 (12)	*

ENTRIES ARE MEANS AND STANDARD ERRORS WITH N OF CASES IN PARENTHESES
W = WILLIAMS TEST OF SIGNIFICANT CONTROL-TREATMENT DIFFERENCES
* CONFIDENCE LEVEL = .95

APPENDIX G (CONCLUDED)

DEPENDENT VARIABLE	TREATMENT GROUPS				
	CONTROL	12.5 MG/KG	W	50 MG/KG	W
WEEK 97	36.8 + .574 (13)	39.9 + .606 (12)		42.9 + 1.13 (12)	*
WEEK 98	34.1 + .783 (13)	37.8 + .729 (12)	*	41.3 + .586 (12)	*
WEEK 99	37.5 + .747 (13)	40.6 + .778 (12)		43.8 + .867 (12)	*
WEEK 100	35.3 + .633 (13)	39.2 + .698 (12)	*	44.9 + .795 (11)	*
WEEK 101	37.3 + .647 (13)	40.7 + .545 (12)		43.8 + 1.12 (12)	*
WEEK 102	32.3 + .653 (13)	38.2 + .583 (12)	*	44.0 + .868 (12)	*
WEEK 103	37.2 + .787 (13)	40.1 + .545 (12)		41.9 + .927 (12)	*
WEEK 104	35.0 + .830 (13)	37.1 + .693 (12)		41.5 + .843 (12)	*

ENTRIES ARE MEANS AND STANDARD ERRORS WITH N OF CAGES IN PARENTHESIS
W = WILLIAMS TEST OF SIGNIFICANT CONTROL-TREATMENT DIFFERENCES
* CONFIDENCE LEVEL = .95

APPENDIX H

AVERAGE WEEKLY BODY WEIGHTS (G) OF MALE RATS
TREATED WITH MAP

DEPENDENT VARIABLE	CONTROL GROUP	TREATMENT GROUPS 12.5 MG/KG	T	R	50 MG/KG	T	R	200 MG/KG	T	R
INITIAL	120.48 + 1.09 (75)	118.49 + 1.07 (70)			117.54 + 1.03 (70)	*		115.91 + .983 (70)	+	
WEEK 1	150.48 + 1.41 (75)	147.64 + 1.27 (70)			138.27 + 1.26 (70)	+		106.84 + 1.28 (70)	+	B
WEEK 2	183.29 + 1.44 (75)	174.14 + 1.57 (70)	+		160.96 + 1.78 (70)	+	A	124.81 + 1.41 (70)	+	B
WEEK 3	212.48 + 1.44 (75)	206.20 + 1.36 (70)	+		189.93 + 1.42 (70)	+	A	142.99 + 1.41 (70)	+	B
WEEK 4	231.91 + 1.46 (75)	226.87 + 1.41 (70)	*		210.13 + 1.33 (70)	+		160.26 + 1.55 (70)	+	B
WEEK 5	249.52 + 1.60 (75)	245.04 + 1.46 (70)	*		226.71 + 1.38 (70)	+		175.43 + 1.59 (70)	+	B
WEEK 6	264.37 + 1.73 (75)	258.57 + 1.64 (70)	+		237.89 + 1.41 (70)	+	A	189.47 + 1.59 (70)	+	B
WEEK 7	274.16 + 1.79 (75)	273.46 + 1.71 (70)			250.53 + 1.54 (70)	+		198.87 + 1.65 (70)	+	B
WEEK 8	288.88 + 1.85 (75)	281.76 + 1.90 (70)	+		258.83 + 1.54 (70)	+	A	205.94 + 1.55 (69)	+	B
WEEK 9	299.65 + 1.91 (75)	293.44 + 1.94 (70)	*		268.23 + 1.61 (70)	+	A	212.42 + 1.80 (69)	+	B
WEEK 10	309.64 + 1.94 (75)	304.63 + 1.88 (70)			276.67 + 1.64 (70)	+	A	219.75 + 1.85 (65)	+	B
WEEK 11	317.28 + 1.98 (75)	311.40 + 2.00 (70)	*		284.19 + 1.75 (70)	+	A	223.70 + 2.36 (64)	+	B
WEEK 12	326.80 + 2.04 (75)	319.04 + 2.05 (70)	+		290.50 + 1.85 (70)	+	A	228.46 + 2.51 (63)	+	B

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ;
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST
10 PERCENT - A, 20 PERCENT - B, 35 PERCENT - C, 50 PERCENT - D. RATIO TEST CANNOT BE CALCULATED - X .

APPENDIX H (CONTINUED)

DEPENDENT VARIABLE	CONTROL GROUP	TREATMENT GROUPS 12.5 MG/KG	T R	50 MG/KG	T R	100 MG/KG †	T R
WEEK 13	334.05 + 2.09 (75)	326.97 + 2.17 (70)	*	298.31 + 1.93 (70)	+ A	243.13 + 3.02 (63)	+ B
WEEK 14	341.19 + 2.14 (75)	334.36 + 2.15 (70)	*	303.09 + 1.94 (70)	+ A	253.29 + 3.17 (63)	+ B
WEEK 15	346.11 + 2.17 (75)	339.87 + 2.24 (70)	*	306.21 + 2.09 (70)	+ A	263.25 + 3.74 (61)	+ B
WEEK 16	351.25 + 2.19 (75)	342.67 + 2.29 (70)	+	311.63 + 2.13 (70)	+ A	267.43 + 3.73 (61)	+ B
WEEK 17	358.08 + 2.23 (75)	348.87 + 2.31 (70)	+	315.26 + 2.24 (70)	+ A	276.63 + 3.88 (59)	+ B
WEEK 18	363.16 + 2.28 (75)	353.26 + 2.40 (70)	+	318.04 + 2.39 (70)	+ A	283.12 + 4.06 (59)	+ B
WEEK 19	368.87 + 2.39 (75)	360.07 + 2.45 (70)	*	323.74 + 2.47 (70)	+ A	287.68 + 4.84 (57)	+ B
WEEK 20	374.77 + 2.43 (75)	365.30 + 2.50 (70)	+	327.99 + 2.55 (70)	+ A	298.06 + 5.20 (52)	+ B
WEEK 21	379.81 + 2.44 (75)	369.23 + 2.57 (70)	+	330.46 + 2.79 (70)	+ A	303.90 + 5.40 (50)	+ A
WEEK 22	383.77 + 2.48 (75)	374.63 + 2.62 (70)	*	334.01 + 2.90 (70)	+ A	308.69 + 5.51 (48)	+ A
WEEK 23	384.77 + 2.53 (75)	374.00 + 2.66 (70)	+	332.44 + 3.08 (70)	+ A	309.49 + 5.68 (47)	+ A
WEEK 24	389.25 + 2.46 (75)	379.51 + 2.76 (70)	+	336.33 + 3.24 (70)	+ A	314.37 + 6.27 (43)	+ A

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
T = TREATMENT-CONTROL CONTRAST ;
R = TREATMENT-CONTROL RATIO TEST : UPPER CONFIDENCE LEVEL LOWER THAN CONTROL MEAN BY AT LEAST
10 PERCENT - A, 20 PERCENT - B, 35 PERCENT - C, 50 PERCENT -D. RATIO TEST CANNOT BE CALCULATED - X.
† DOSE LEVEL REDUCED TO 100 MG/KG/DAY STARTING WITH WEEK 13.

APPENDIX H (CONTINUED)

DEPENDENT VARIABLE	CONTROL GROUP	TREATMENT GROUPS 12.5 MG/KG	T	R	50 MG/KG	T	R	100 MG/KG †	T	R
WEEK 25	393.36 + 2.53 (75)	384.41 + 2.71 (70)	*		342.51 + 3.36 (70)	+	A	320.14 + 7.37 (37)	+	A
WEEK 26	398.61 + 2.54 (75)	389.39 + 2.74 (70)	*		344.50 + 3.56 (70)	+	A	327.85 + 7.80 (34)	+	A
WEEK 27	399.61 + 2.54 (75)	390.01 + 2.74 (70)	*		347.34 + 3.58 (70)	+	A	333.80 + 8.45 (30)	+	A
WEEK 28	403.80 + 2.59 (75)	395.34 + 2.67 (70)	*		351.54 + 3.77 (70)	+	A	336.78 + 9.64 (27)	+	A
WEEK 29	409.23 + 2.67 (75)	400.06 + 2.77 (70)	*		353.59 + 3.86 (70)	+	A	344.52 + 10.4 (25)	+	A
WEEK 30	412.27 + 2.69 (75)	403.46 + 2.84 (70)	*		355.67 + 3.78 (70)	+	A	349.96 + 10.1 (24)	+	A
WEEK 31	413.83 + 2.73 (75)	406.04 + 2.85 (70)	*		356.37 + 4.11 (70)	+	A	355.30 + 9.89 (23)	+	A
WEEK 32	416.85 + 2.72 (75)	407.51 + 2.81 (70)	*		357.34 + 4.02 (70)	+	A	362.10 + 9.24 (21)	+	A
WEEK 33	421.31 + 2.77 (75)	410.46 + 2.93 (70)	+		359.53 + 4.20 (70)	+	A	365.84 + 8.13 (19)	+	A
WEEK 34	426.39 + 2.81 (75)	414.77 + 2.98 (70)	+		361.64 + 4.15 (69)	+	A			
WEEK 35	429.20 + 2.79 (75)	417.61 + 2.92 (70)	+		360.96 + 4.25 (69)	+	A			
WEEK 36	433.15 + 2.81 (75)	420.57 + 2.95 (70)	+		362.19 + 4.14 (69)	+	A			

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
T = TREATMENT-CONTROL CONTRAST ;
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 PERCENT - A, 20 PERCENT - B, 35 PERCENT - C, 50 PERCENT - D. RATIO TEST CANNOT BE CALCULATED - X .
† HIGH DOSE TERMINATED AFTER 33 WEEKS ON TEST.

DEPENDENT VARIABLE	CONTROL GROUP	TREATMENT GROUPS 12.5 MG/KG	T	R	50 MG/KG	T	R
WEEK 37	437.16 + 2.82 (75)	421.91 + 3.01 (70)	+		359.99 + 3.86 (67)	+	A
WEEK 38	441.64 + 2.92 (75)	426.31 + 3.03 (70)	+		362.68 + 4.03 (66)	+	A
WEEK 39	442.85 + 2.89 (75)	427.71 + 3.14 (70)	+		362.86 + 3.91 (66)	+	A
WEEK 40	443.77 + 2.95 (75)	429.11 + 3.22 (70)	+		368.28 + 3.91 (65)	+	A
WEEK 41	447.27 + 2.94 (75)	432.31 + 3.15 (70)	+		368.54 + 3.95 (65)	+	A
WEEK 42	448.95 + 2.87 (75)	433.74 + 3.20 (70)	+		368.34 + 4.15 (64)	+	A
WEEK 43	450.08 + 2.96 (75)	435.21 + 3.17 (70)	+		372.42 + 4.11 (64)	+	A
WEEK 44	454.17 + 2.92 (75)	440.57 + 3.17 (70)	+		377.27 + 4.16 (64)	+	A
WEEK 45	457.27 + 2.98 (75)	443.80 + 3.42 (70)	+		380.72 + 4.32 (64)	+	A
WEEK 46	456.01 + 3.01 (75)	442.21 + 3.39 (70)	+		383.51 + 4.27 (61)	+	A
WEEK 47	460.70 + 3.03 (74)	444.77 + 3.26 (70)	+		384.72 + 4.36 (61)	+	A
WEEK 48	461.76 + 3.08 (74)	446.17 + 3.29 (70)	+		384.17 + 4.48 (59)	+	A

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ;
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 PERCENT - A, 20 PERCENT - B, 35 PERCENT - C, 50 PERCENT - D. RATIO TEST CANNOT BE CALCULATED - X.

APPENDIX H (CONTINUED)

DEPENDENT VARIABLE	CONTROL GROUP	TREATMENT GROUPS				
		12.5 MG/KG	T	R	50 MG/KG	T R
WEEK 49	459.70 + 3.01 (74)	445.03 + 3.24 (70)	+		383.53 + 4.58 (59)	+ A
WEEK 50	462.68 + 2.94 (74)	446.79 + 3.51 (70)	+		385.29 + 4.51 (58)	+ A
WEEK 51	465.43 + 3.06 (74)	450.89 + 3.38 (70)	+		388.30 + 4.56 (57)	+ A
WEEK 52	463.45 + 2.95 (74)	448.57 + 3.36 (70)	+		387.63 + 4.50 (57)	+ A
WEEK 53	467.05 + 3.36 (64)	454.55 + 3.24 (60)	+		393.57 + 5.42 (49)	+ A
WEEK 54	468.67 + 3.23 (64)	453.70 + 3.27 (60)	+		391.08 + 5.22 (49)	+ A
WEEK 55	467.11 + 3.48 (64)	455.05 + 3.23 (60)	*		390.94 + 4.98 (47)	+ A
WEEK 56	463.41 + 3.30 (64)	449.58 + 3.09 (60)	+		388.69 + 5.10 (45)	+ A
WEEK 57	466.94 + 3.38 (64)	453.13 + 3.31 (60)	+		392.33 + 5.19 (45)	+ A
WEEK 58	469.11 + 3.39 (64)	454.12 + 3.39 (60)	+		393.41 + 4.91 (44)	+ A
WEEK 59	471.41 + 3.43 (64)	457.55 + 3.39 (60)	+		397.17 + 5.12 (42)	+ A
WEEK 60	471.36 + 3.39 (64)	458.35 + 3.39 (60)	+		395.56 + 4.80 (41)	+ A

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ;
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVALS GREATER OR LOWER THAN CONTROL MEANS BY AT LEAST
10 PERCENT - A, 20 PERCENT - B, 35 PERCENT - C, 50 PERCENT - D. RATIO TEST CANNOT BE CALCULATED - X.

APPENDIX H (CONTINUED)

DEPENDENT VARIABLE	TREATMENT GROUPS: CONTROL GROUP	12.5 MG/KG	T	R	50 MG/KG	T	R
WEEK 61	475.56 + 3.42 (64)	461.30 + 3.39 (60)	+		396.39 + 4.58 (41)	+	A
WEEK 62	475.05 + 3.36 (64)	461.12 + 3.32 (60)	+		396.12 + 4.74 (41)	+	A
WEEK 63	479.19 + 3.34 (64)	462.92 + 3.41 (60)	+		396.69 + 5.14 (39)	+	A
WEEK 64	480.68 + 3.47 (63)	463.20 + 3.48 (60)	+		394.46 + 5.29 (39)	+	A
WEEK 65	477.56 + 3.79 (62)	461.28 + 3.68 (60)	+		394.77 + 5.08 (39)	+	A
WEEK 66	482.31 + 3.93 (62)	464.05 + 3.64 (60)	+		396.56 + 5.09 (39)	+	A
WEEK 67	479.15 + 3.65 (61)	464.63 + 3.61 (60)	+		398.49 + 5.01 (39)	+	A
WEEK 68	477.72 + 3.62 (61)	463.48 + 3.64 (60)	+		398.31 + 4.95 (39)	+	A
WEEK 69	478.80 + 3.65 (61)	463.98 + 3.73 (60)	+		400.54 + 5.07 (39)	+	A
WEEK 70	479.08 + 3.77 (60)	463.12 + 3.67 (60)	+		402.97 + 4.74 (38)	+	A
WEEK 71	482.60 + 3.72 (60)	465.63 + 3.73 (60)	+		401.61 + 5.02 (38)	+	A
WEEK 72	483.47 + 3.68 (60)	465.03 + 3.79 (60)	+		403.11 + 5.04 (36)	+	A

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
T = TREATMENT-CONTROL CONTRAST;
R = TREATMENT-CONTROL RATIO TEST : UPPER CONFIDENCE LEVEL LOWER THAN CONTROL MEAN BY AT LEAST
10 PERCENT - A, 20 PERCENT - B, 35 PERCENT - C, 50 PERCENT - D. RATIO TEST CANNOT BE CALCULATED - X.

DEPENDENT VARIABLE	CONTROL GROUP	TREATMENT GROUPS 12.5 MG/KG	T	R	50 MG/KG	T	R
WEEK 73	483.73 + 3.70 (60)	465.18 + 3.81 (60)	+		403.35 + 5.32 (31)	+	A
WEEK 74	483.10 + 3.94 (60)	465.48 + 3.90 (60)	+		403.48 + 5.81 (31)	+	A
WEEK 75	484.72 + 3.88 (60)	464.32 + 3.84 (60)	+		404.66 + 5.41 (29)	+	A
WEEK 76	484.12 + 3.94 (60)	463.72 + 3.79 (60)	+		406.41 + 5.55 (29)	+	A
WEEK 77	484.47 + 3.93 (60)	463.40 + 3.91 (60)	+		407.14 + 5.87 (28)	+	A
WEEK 78	485.15 + 3.94 (60)	465.17 + 3 93 (59)	+		409.44 + 5.57 (27)	+	A
WEEK 79	482.77 + 4.26 (60)	464.93 + 4.01 (50)	+		407.16 + 6.10 (25)	+	A
WEEK 80	483.10 + 4.78 (60)	462.69 + 3.96 (59)	+		409.24 + 6.00 (25)	+	A
WEEK 81	487.05 + 3.99 (59)	463.83 + 3.93 (50)	+		409.12 + 6.05 (25)	+	A
WEEK 82	484.95 + 3.97 (50)	461.49 + 4.26 (59)	+		408.04 + 5.99 (24)	+	A
WEEK 83	485.14 + 3.96 (50)	463.60 + 3.89 (58)	+		408.33 + 5.77 (24)	+	A
WEEK 84	483.68 + 4.07 (59)	461.29 + 4.10 (58)	+		407.75 + 6.27 (24)	+	A

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
T = TREATMENT-CONTROL CONTRAST ;
R = TREATMENT-CONTROL RATIO TEST : UPPER CONFIDENCE LEVEL LOWER THAN CONTROL MEAN BY AT LEAST 10 PERCENT - A, 20 PERCENT - B, 35 PERCENT - C, 50 PERCENT - D. RATIO TEST CANNOT BE CALCULATED - X.

APPENDIX H (CONTINUED)

DEPENDENT VARIABLE	TREATMENT GROUPS: CONTROL GROUP	12.5 MG/KG	T	R	50 MG/KG	T	R
WEEK 85	484.98 + 4.11 (59)	461.17 + 4.21 (58)	+		405.64 + 6.50 (22)	+	A
WEEK 86	484.56 + 4.05 (59)	457.55 + 4.10 (58)	+		404.45 + 6.36 (22)	+	A
WEEK 87	484.31 + 4.04 (59)	460.82 + 3.95 (57)	+		406.09 + 5.95 (22)	+	A
WEEK 88	483.00 + 4.18 (59)	460.32 + 3.88 (57)	+		407.10 + 6.08 (21)	+	A
WEEK 89	475.71 + 4.88 (59)	455.96 + 3.79 (57)	+		401.84 + 6.80 (19)	+	A
WEEK 90	480.16 + 4.46 (57)	455.21 + 3.81 (57)	+		403.26 + 6.62 (19)	+	A
WEEK 91	479.93 + 4.74 (57)	456.09 + 3.83 (57)	+		401.47 + 6.66 (19)	+	A
WEEK 92	476.98 + 4.51 (56)	450.47 + 3.99 (57)	+		396.68 + 7.02 (19)	+	A
WEEK 93	481.27 + 4.81 (56)	454.32 + 3.96 (57)	+		401.42 + 6.71 (19)	+	A
WEEK 94	479.41 + 4.85 (56)	452.46 + 3.97 (57)	+		401.00 + 6.45 (19)	+	A
WEEK 95	479.64 + 5.08 (55)	450.67 + 4.15 (57)	+		398.84 + 7.04 (19)	+	A
WEEK 96	479.35 + 4.62 (54)	450.55 + 4.09 (56)	+		398.53 + 6.57 (19)	+	A

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
T = TREATMENT-CONTROL CONTRAST ;
R = TREATMENT-CONTROL RATIO TEST : UPPER CONFIDENCE LEVEL LOWER THAN CONTROL MEAN BY AT LEAST 10 PERCENT - A, 20 PERCENT - B, 35 PERCENT - C, 50 PERCENT - D. RATIO TEST CANNOT BE CALCULATED - X.

APPENDIX H (CONCLUDED)

DEPENDENT VARIABLE	TREATMENT GROUPS: CONTROL GROUP	12.5 MG/KG	T	R	50 MG/KG	T	R
WEEK 97	476.64 + 4.69 (53)	450.05 + 3.96 (55)	+		394.33 + 7.80 (18)	+	A
WEEK 98	478.73 + 4.79 (52)	449.76 + 3.93 (55)	+		392.31 + 7.29 (16)	+	A
WEEK 99	474.38 + 5.00 (52)	444.73 + 4.01 (55)	+		390.44 + 6.83 (16)	+	A
WEEK 100	469.90 + 4.99 (51)	440.50 + 3.92 (54)	+		388.31 + 6.80 (16)	+	A
WEEK 101	471.29 + 5.15 (49)	440.70 + 4.17 (53)	+		386.81 + 7.18 (16)	+	A
WEEK 102	466.70 + 5.08 (47)	438.10 + 4.15 (49)	+		376.50 + 7.73 (14)	+	A
WEEK 103	462.64 + 5.17 (47)	434.00 + 4.12 (49)	+		376.46 + 8.56 (13)	+	A
WEEK 104	461.34 + 5.36 (47)	430.98 + 4.30 (49)	+		369.15 + 7.89 (13)	+	A

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
T = TREATMENT-CONTROL CONTRAST;
R = TREATMENT-CONTROL RATIO TEST : UPPER CONFIDENCE LEVEL LOWER THAN CONTROL MEAN BY AT LEAST 10 PERCENT - A, 20 PERCENT - B, 35 PERCENT - C, 50 PERCENT - D. RATIO TEST CANNOT BE CALCULATED - X.

APPENDIX I

AVERAGE WEEKLY BODY WEIGHTS (G) OF FEMALE RATS TREATED WITH NAP

DEPENDENT VARIABLE	CONTROL GROUP	TREATMENT GROUPS							
		12.5 MG/KG	T	R	50 MG/KG	T	R	200 MG/KG	T	R
INITIAL	94.27 + .750 (75)	93.59 + .731 (70)			93.24 + .706 (70)			92.39 + .639 (70)		
WEEK 1	105.17 + 1.14 (75)	109.14 + .852 (70)	+		103.74 + .777 (70)			85.34 + .633 (70)	+	A
WEEK 2	120.29 + 1.44 (75)	116.83 + 1.15 (70)			111.56 + 1.16 (70)	+		93.64 + .869 (70)	+	B
WEEK 3	133.92 + .926 (75)	131.86 + .817 (70)			125.90 + .778 (70)	+		102.24 + .757 (70)	+	B
WEEK 4	144.16 + .860 (75)	141.44 + .842 (70)	*		132.61 + .751 (70)	+		110.11 + .770 (70)	+	B
WEEK 5	152.84 + .883 (75)	148.90 + .931 (70)	+		139.66 + .888 (70)	+		1.7.51 + .817 (70)	+	B
WEEK 6	158.64 + 1.03 (75)	154.46 + .994 (70)	+		144.31 + .886 (70)	+		123.63 + .875 (70)	+	B
WEEK 7	161.92 + .944 (74)	160.64 + 1.01 (70)			149.49 + .887 (70)	+		129.49 + .946 (70)	+	B
WEEK 8	168.91 + .979 (74)	164.31 + 1.07 (70)	+		151.69 + .909 (70)	+	A	134.30 + 1.01 (70)	+	B
WEEK 9	174.45 + 1.06 (74)	167.40 + 1.02 (70)	+		155.16 + .914 (70)	+	A	140.39 + 1.18 (70)	+	A
WEEK 10	177.91 + .966 (74)	172.04 + 1.09 (70)	+		159.30 + .928 (70)	+	A	146.61 + 1.25 (70)	+	A
WEEK 11	181.11 + 1.01 (74)	173.50 + 1.09 (70)	+		161.36 + .994 (70)	+	A	152.74 + 1.34 (69)	+	A
WEEK 12	182.96 + .991 (74)	176.20 + 1.11 (70)	+		162.74 + 1.00 (70)	+	A	157.70 + 1.50 (69)	+	A

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ;
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 PERCENT - A, 20 PERCENT - B, 35 PERCENT - C, 50 PERCENT - D. RATIO TEST CANNOT BE CALCULATED - X .

APPENDIX I (CONTINUED)

DEPENDENT VARIABLE	TREATMENT GROUPS								
	CONTROL GROUP	12.5 MG/KG	T	R	50 MG/KG	T	R	100 MG/KG †	T	R
WEEK 13	186.77 ± .986 (74)	178.97 ± 1.07 (70)	♦		167.44 ± 1.02 (70)	♦	A	166.72 ± 1.39 (69)	♦	A
WEEK 14	189.32 ± 1.01 (74)	181.23 ± 1.09 (70)	♦		168.44 ± 1.11 (70)	♦	A	171.83 ± 1.55 (69)	♦	
WEEK 15	190.74 ± 1.03 (74)	183.67 ± 1.09 (70)	♦		168.99 ± 1.17 (70)	♦	A	179.43 ± 1.60 (69)	♦	
WEEK 16	192.43 ± 1.03 (74)	184.11 ± 1.09 (70)	♦		171.96 ± 1.22 (70)	♦	A	182.07 ± 1.64 (69)	♦	
WEEK 17	195.14 ± 1.00 (74)	186.37 ± 1.09 (70)	♦		173.63 ± 1.21 (70)	♦	A	185.58 ± 1.61 (69)	♦	
WEEK 18	195.84 ± .994 (74)	185.71 ± 1.11 (70)	♦		173.83 ± 1.29 (70)	♦	A	190.75 ± 1.81 (69)	*	
WEEK 19	198.31 ± 1.03 (74)	190.01 ± 1.11 (70)	♦		176.00 ± 1.23 (70)	♦	A	193.87 ± 1.91 (69)	*	
WEEK 20	200.51 ± 1.09 (74)	191.87 ± 1.16 (70)	♦		178.27 ± 1.35 (70)	♦	A	200.58 ± 2.02 (69)		
WEEK 21	202.11 ± 1.08 (74)	193.20 ± 1.15 (70)	♦		177.17 ± 1.27 (70)	♦	A	202.23 ± 2.11 (69)		
WEEK 22	202.99 ± 1.14 (74)	194.11 ± 1.17 (70)	♦		178.94 ± 1.36 (70)	♦	A	206.51 ± 2.22 (69)		
WEEK 23	202.35 ± 1.14 (74)	193.07 ± 1.10 (70)	♦		179.27 ± 1.37 (70)	♦	A	208.10 ± 2.28 (69)	*	
WEEK 24	202.99 ± 1.15 (74)	194.59 ± 1.15 (70)	♦		181.06 ± 1.38 (70)	♦	A	212.68 ± 2.30 (69)	♦	

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
♦ CONFIDENCE LEVEL = .99
T = TREATMENT-CONTROL CONTRAST ;
R = TREATMENT-CONTROL RATIO TEST : UPPER CONFIDENCE LEVEL LOWER THAN CONTROL MEAN BY AT LEAST
10 PERCENT - A, 20 PERCENT - B, 35 PERCENT - C, 50 PERCENT -D. RATIO TEST CANNOT BE CALCULATED - X.
† DOSE LEVEL REDUCED TO 100 MG/KG/DAY STARTING WITH WEEK 13.

APPENDIX I (CONTINUED)

DEPENDENT VARIABLE	CONTROL GROUP	TREATMENT GROUPS							
		12.5 MG/KG	T	R	50 MG/KG	T	R	100 MG/KG †	T R
WEEK 25	204.68 ± 1.13 (74)	193.46 ± 1.20 (70)	♦		181.80 ± 1.40 (70)	♦	A	216.13 ± 2.40 (69)	♦
WEEK 26	206.11 ± 1.14 (74)	196.43 ± 1.14 (70)	♦		183.26 ± 1.47 (70)	♦	A	219.54 ± 2.35 (69)	♦
WEEK 27	205.84 ± 1.17 (74)	195.66 ± 1.16 (70)	♦		183.66 ± 1.49 (70)	♦	A	221.09 ± 2.48 (69)	♦
WEEK 28	207.53 ± 1.17 (74)	198.27 ± 1.16 (70)	♦		185.17 ± 1.50 (70)	♦	A	224.55 ± 2.44 (69)	♦
WEEK 29	210.19 ± 1.23 (74)	200.07 ± 1.17 (70)	♦		186.86 ± 1.63 (70)	♦	A	227.46 ± 2.39 (69)	♦
WEEK 30	212.11 ± 1.23 (74)	201.97 ± 1.19 (70)	♦		189.01 ± 1.75 (70)	♦	A	227.61 ± 2.34 (69)	♦
WEEK 31	213.80 ± 1.26 (74)	202.49 ± 1.19 (70)	♦		189.31 ± 1.86 (70)	♦	A	229.20 ± 2.36 (69)	♦
WEEK 32	214.50 ± 1.32 (74)	202.24 ± 1.23 (70)	♦		188.49 ± 1.99 (70)	♦	A	230.06 ± 2.48 (69)	♦
WEEK 33	216.27 ± 1.30 (74)	203.49 ± 1.23 (70)	♦		188.86 ± 2.00 (70)	♦	A	231.22 ± 2.35 (69)	♦
WEEK 34	219.38 ± 1.30 (74)	205.50 ± 1.21 (70)	♦		191.94 ± 2.09 (70)	♦	A		
WEEK 35	221.20 ± 1.32 (74)	208.46 ± 1.29 (70)	♦		194.64 ± 2.17 (70)	♦	A		
WEEK 36	222.47 ± 1.36 (74)	208.56 ± 1.25 (70)	♦		196.24 ± 2.36 (70)	♦	A		

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
♦ CONFIDENCE LEVEL = .99
T = TREATMENT-CONTROL CONTRAST ;
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 PERCENT - A, 20 PERCENT - B, 35 PERCENT - C, 50 PERCENT - D. RATIO TEST CANNOT BE CALCULATED - X .
† HIGH DOSE TERMINATED AFTER 33 WEEKS ON TEST.

APPENDIX I (CONTINUED)

DEPENDENT VARIABLE	CONTROL GROUP	TREATMENT GROUPS 12.5 MG/KG	T R	50 MG/KG	T R
WEEK 37	224.61 + 1.47 (74)	208.59 + 1.30 (70)	+	196.59 + 2.36 (70)	+ A
WEEK 38	227.93 + 1.52 (74)	212.43 + 1.34 (70)	+	200.33 + 2.47 (70)	+ A
WEEK 39	228.45 + 1.50 (74)	212.76 + 1.36 (70)	+	201.26 + 2.51 (70)	+ A
WEEK 40	228.95 + 1.57 (74)	211.57 + 1.30 (70)	+	202.46 + 2.57 (70)	+ A
WEEK 41	231.09 + 1.63 (74)	213.44 + 1.32 (70)	+	204.77 + 2.54 (70)	+ A
WEEK 42	231.68 + 1.61 (74)	213.57 + 1.33 (70)	+	206.01 + 2.67 (70)	+ A
WEEK 43	232.88 + 1.58 (74)	214.57 + 1.35 (70)	+	205.46 + 2.53 (70)	+ A
WEEK 44	234.49 + 1.62 (74)	215.66 + 1.38 (70)	+	207.83 + 2.72 (70)	+ A
WEEK 45	236.70 + 1.67 (74)	218.59 + 1.39 (70)	+	211.30 + 2.73 (70)	+ A
WEEK 46	237.05 + 1.79 (74)	217.50 + 1.36 (70)	+	211.20 + 2.84 (70)	+ A
WEEK 47	238.84 + 1.76 (74)	219.26 + 1.35 (70)	+	210.81 + 2.84 (70)	+ A
WEEK 48	240.96 + 1.83 (74)	219.17 + 1.46 (69)	+	212.19 + 2.97 (70)	+ A

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARNETHESES
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ;
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 PERCENT - A, 20 PERCENT - B, 35 PERCENT - C, 50 PERCENT - D. RATIO TEST CANNOT BE CALCULATED - X.

APPENDIX I (CONTINUED)

DEPENDENT VARIABLE	CONTROL GROUP	TREATMENT GROUPS 12.5 MG/KG	T	R	50 MG/KG	T	R
WEEK 49	239.80 + 1.87 (74)	218.64 + 1.48 (69)	+		211.11 + 3.17 (70)	+	A
WEEK 50	241.89 + 1.89 (74)	221.71 + 1.47 (69)	+		217.17 + 3.08 (70)	+	A
WEEK 51	244.54 + 1.95 (74)	222.68 + 1.53 (69)	+		218.80 + 3.12 (70)	+	A
WEEK 52	243.41 + 1.96 (74)	221.36 + 1.62 (69)	+		217.83 + 2.99 (70)	+	A
WEEK 53	248.16 + 2.30 (64)	226.63 + 1.77 (59)	+		225.02 + 3.33 (60)	+	
WEEK 54	249.59 + 2.34 (64)	226.41 + 1.79 (59)	+		224.03 + 3.33 (60)	+	A
WEEK 55	251.64 + 2.36 (64)	228.83 + 1.79 (59)	+		226.72 + 3.39 (60)	+	
WEEK 56	250.87 + 2.38 (63)	227.61 + 1.89 (59)	+		226.60 + 3.30 (60)	+	
WEEK 57	253.10 + 2.43 (63)	228.93 + 1.98 (59)	+		227.03 + 3.19 (60)	+	A
WEEK 58	254.02 + 2.53 (63)	226.95 + 2.01 (59)	+	A	227.53 + 3.26 (60)	+	A
WEEK 59	256.35 + 2.64 (63)	229.39 + 2.19 (59)	+	A	231.43 + 3.33 (60)	+	
WEEK 60	258.17 + 2.56 (63)	230.56 + 2.19 (59)	+	A	232.05 + 3.20 (60)	+	A

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ;
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEANS BY AT LEAST
10 PERCENT - A, 20 PERCENT - B, 35 PERCENT - C, 50 PERCENT - D. RATIO TEST CANNOT BE CALCULATED - X.

APPENDIX I (CONTINUED)

DEPENDENT VARIABLE	CONTROL GROUP	TREATMENT GROUPS 12.5 MG/KG	T	R	50 MG/KG	T	R
WEEK 61	264.84 + 2.67 (63)	233.34 + 2.25 (59)	+	A	234.07 + 3.26 (60)	+	A
WEEK 62	266.13 + 2.75 (63)	234.00 + 2.28 (59)	+	A	236.03 + 3.20 (60)	+	A
WEEK 63	269.10 + 2.83 (63)	238.15 + 2.18 (59)	+	A	237.10 + 3.15 (60)	+	A
WEEK 64	271.83 + 2.81 (63)	239.12 + 2.39 (59)	+	A	238.45 + 3.17 (60)	+	A
WEEK 65	272.71 + 2.93 (63)	240.29 + 2.35 (58)	+	A	235.42 + 3.18 (60)	+	A
WEEK 66	275.40 + 2.96 (63)	242.95 + 2.40 (58)	+	A	238.60 + 3.21 (60)	+	A
WEEK 67	277.29 + 2.90 (63)	245.50 + 2.54 (58)	+	A	239.53 + 3.03 (60)	+	A
WEEK 68	275.59 + 3.18 (63)	245.60 + 2.49 (58)	+	A	241.32 + 2.90 (60)	+	A
WEEK 69	280.27 + 3.01 (63)	248.72 + 2.51 (58)	+	A	244.20 + 3.13 (60)	+	A
WEEK 70	282.17 + 2.94 (63)	249.02 + 2.53 (58)	+	A	244.07 + 3.04 (58)	+	A
WEEK 71	285.76 + 3.04 (63)	251.78 + 2.53 (58)	+	A	245.38 + 3.12 (58)	+	A
WEEK 72	287.21 + 3.05 (63)	253.90 + 2.57 (58)	+	A	246.53 + 2.98 (58)	+	A

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
T = TREATMENT-CONTROL CONTRAST;
R = TREATMENT-CONTROL RATIO TEST : UPPER CONFIDENCE LEVEL LOWER THAN CONTROL MEAN BY AT LEAST 10 PERCENT - A, 20 PERCENT - B, 35 PERCENT - C, 50 PERCENT - D. RATIO TEST CANNOT BE CALCULATED - X.

APPENDIX I (CONTINUED)

DEPENDENT VARIABLE	CONTROL GROUP	TREATMENT GROUPS 12.5 MG/KG	T	R	50 MG/KG	T	R
WEEK 73	289.92 + 3.12 (61)	255.72 + 2.68 (58)	+	A	245.69 + 3.08 (58)	+	A
WEEK 74	290.38 + 3.03 (61)	257.10 + 2.67 (58)	+	A	248.31 + 3.04 (58)	+	A
WEEK 75	291.82 + 3.07 (61)	257.33 + 2.72 (58)	+	A	245.78 + 2.78 (58)	+	A
WEEK 76	292.34 + 3.09 (61)	259.59 + 2.90 (58)	+	A	249.00 + 3.00 (58)	+	A
WEEK 77	295.00 + 3.54 (61)	259.07 + 2.57 (57)	+	A	249.26 + 2.87 (58)	+	A
WEEK 78	297.43 + 3.66 (61)	261.18 + 2.63 (57)	+	A	250.74 + 2.95 (58)	+	A
WEEK 79	298.00 + 3.19 (60)	261.93 + 2.67 (57)	+	A	250.05 + 2.98 (58)	+	A
WEEK 80	300.32 + 3.05 (60)	264.47 + 2.98 (57)	+	A	252.33 + 3.14 (58)	+	A
WEEK 81	302.18 + 2.99 (60)	265.89 + 2.80 (57)	+	A	253.77 + 2.96 (57)	+	A
WEEK 82	303.10 + 2.93 (60)	267.09 + 2.98 (57)	+	A	252.88 + 3.01 (57)	+	A
WEEK 83	306.05 + 3.07 (60)	268.96 + 3.27 (56)	+	A	255.21 + 3.10 (56)	+	A
WEEK 84	306.98 + 3.03 (60)	270.87 + 3.16 (55)	+	A	252.82 + 2.98 (56)	+	A

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
T = TREATMENT-CONTROL CONTRAST ;
R = TREATMENT-CONTROL RATIO TEST : UPPER CONFIDENCE LEVEL LOWER THAN CONTROL MEAN BY AT LEAST
10 PERCENT - A, 20 PERCENT - B, 35 PERCENT - C, 50 PERCENT - D. RATIO TEST CANNOT BE CALCULATED - X.

APPENDIX I (CONTINUED)

DEPENDENT VARIABLE	CONTROL GROUP	TREATMENT GROUPS 12.5 MG/KG	T	R	50 MG/KG	T	R
WEEK 85	308.87 + 2.94 (60)	270.96 + 3.15 (55)	+	A	255.54 + 3.06 (56)	+	A
WEEK 86	307.82 + 2.87 (60)	271.60 + 3.09 (55)	+	A	253.95 + 2.98 (56)	+	A
WEEK 87	308.08 + 3.15 (59)	273.65 + 3.17 (55)	+	A	254.79 + 3.07 (56)	+	A
WEEK 88	309.42 + 3.12 (59)	274.28 + 3.28 (54)	+	A	255.73 + 2.92 (56)	+	A
WEEK 89	309.37 + 3.28 (59)	271.17 + 3.32 (54)	+	A	254.33 + 3.26 (55)	+	A
WEEK 90	308.63 + 3.19 (59)	270.37 + 3.26 (54)	+	A	256.76 + 3.20 (54)	+	A
WEEK 91	310.58 + 3.29 (59)	271.67 + 3.51 (54)	+	A	257.23 + 3.22 (52)	+	A
WEEK 92	308.41 + 3.12 (59)	270.76 + 3.56 (54)	+	A	258.21 + 3.22 (52)	+	A
WEEK 93	311.95 + 3.32 (59)	274.23 + 3.04 (53)	+	A	258.77 + 3.12 (52)	+	A
WEEK 94	309.98 + 3.69 (59)	275.49 + 3.03 (53)	+	A	259.16 + 3.35 (51)	+	A
WEEK 95	311.12 + 3.51 (58)	274.60 + 3.54 (52)	+	A	257.73 + 3.23 (51)	+	A
WEEK 96	311.00 + 3.55 (57)	278.43 + 3.16 (47)	+	A	261.12 + 3.44 (51)	+	A

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
T = TREATMENT-CONTROL CONTRAST ;
R = TREATMENT-CONTROL RATIO TEST : UPPER CONFIDENCE LEVEL LOWER THAN CONTROL MEAN BY AT LEAST 10 PERCENT - A, 20 PERCENT - B, 35 PERCENT - C, 50 PERCENT - D. RATIO TEST CANNOT BE CALCULATED - X.

APPENDIX I (CONCLUDED)

DEPENDENT VARIABLE	CONTROL GROUP	TREATMENT GROUPS				
		12.5 MG/KG	T	R	50 MG/KG	T R
WEEK 97	311.98 + 3.47 (56)	276.98 + 3.24 (46)	+	A	259.69 + 3.34 (51)	+ A
WEEK 98	314.29 + 3.63 (55)	278.93 + 3.63 (46)	+	A	261.80 + 3.38 (50)	+ A
WEEK 99	313.06 + 3.44 (54)	279.31 + 3.52 (45)	+	A	258.40 + 3.74 (50)	+ A
WEEK 100	310.58 + 3.49 (53)	278.25 + 3.12 (44)	+	A	259.40 + 3.82 (50)	+ A
WEEK 101	311.08 + 3.76 (51)	279.91 + 3.22 (44)	+	A	258.57 + 3.38 (49)	+ A
WEEK 102	306.78 + 3.78 (50)	277.58 + 3.46 (43)	+		257.90 + 3.39 (49)	+ A
WEEK 103	306.61 + 3.81 (49)	276.74 + 3.63 (43)	+		256.60 + 3.33 (47)	+ A
WEEK 104	306.10 + 3.90 (49)	276.26 + 3.72 (42)	+		257.00 + 3.53 (47)	+ A

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
T = TREATMENT-CONTROL CONTRAST;
R = TREATMENT-CONTROL RATIO TEST : UPPER CONFIDENCE LEVEL LOWER THAN CONTROL MEAN BY AT LEAST 10 PERCENT - A, 20 PERCENT - B, 35 PERCENT - C, 50 PERCENT - D. RATIO TEST CANNOT BE CALCULATED - X.

APPENDIX J

AVERAGE WEEKLY BODY WEIGHT GAIN (G) OF MALE RATS
TREATED WITH MAP

DEPENDENT VARIABLE	CONTROL GROUP	TREATMENT GROUPS 12.5 MG/KG	T	R	50 MG/KG	T	R	200 MG/KG	T	R
WEEK 1	30.00 + .603 (75)	29.16 + .711 (70)			20.73 + .655 (70)	+	B	-9.07 + .929 (70)	+	D
WEEK 2	32.81 + .615 (75)	26.50 + 1.08 (70)	+	A	22.69 + 1.37 (70)	+	B	17.97 + .888 (70)	+	C
WEEK 3	29.19 + .602 (75)	32.06 + .636 (70)	+		28.97 + .942 (70)			18.17 + .569 (70)	+	C
WEEK 4	19.43 + .378 (75)	20.67 + .526 (70)			20.20 + .516 (70)			17.27 + .505 (70)	+	A
WEEK 5	17.61 + .399 (75)	18.17 + .548 (70)			16.59 + .428 (70)			15.17 + .496 (70)	+	A
WEEK 6	14.85 + .357 (75)	13.53 + .404 (70)	*		11.17 + .324 (70)	+	B	14.04 + .476 (70)		
WEEK 7	9.79 + .431 (75)	14.89 + .314 (70)	+	D	12.64 + .449 (70)	+	B	9.40 + .545 (70)		
WEEK 8	14.72 + .374 (75)	8.30 + .531 (70)	+	C	8.30 + .406 (70)	+	C	7.20 + .532 (69)	+	D
WEEK 9	10.77 + .273 (75)	11.69 + .513 (70)			9.40 + .387 (70)	+	A	6.48 + .780 (69)	+	C
WEEK 10	9.99 + .356 (75)	11.19 + .458 (70)	*	A	8.44 + .362 (70)	+	A	5.82 + .822 (65)	+	C
WEEK 11	7.64 + .345 (75)	6.77 + .420 (70)		A	7.51 + .404 (70)			3.73 + .921 (64)	+	D
WEEK 12	9.52 + .373 (75)	7.64 + .393 (70)	+	A	6.31 + .468 (70)	+	B	4.52 + .990 (63)	+	D

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ;
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST
10 PERCENT - A, 20 PERCENT - B, 35 PERCENT - C, 50 PERCENT - D. RATIO TEST CANNOT BE CALCULATED - X .

APPENDIX J (CONTINUED)

DEPENDENT VARIABLE	CONTROL GROUP	TREATMENT GROUPS 12.5 MG/KG	T	R	50 MG/KG	T	R	100 MG/KG †	T	R
WEEK 13	7.25 + .382 (75)	7.93 + .387 (70)			7.81 + .365 (70)			14.67 + 1.18 (63)	+	D
WEEK 14	7.13 + .349 (75)	7.39 + .356 (70)			4.77 + .405 (70)	+	B	10.16 + 1.06 (63)	+	C
WEEK 15	4.92 + .325 (75)	5.51 + .324 (70)		A	3.13 + .513 (70)	+	C	9.54 + 1.23 (61)	+	D
WEEK 16	5.15 + .371 (75)	2.80 + .375 (70)	+	C	5.41 + .470 (70)			4.18 + 1.04 (61)		A
WEEK 17	6.83 + .403 (75)	6.20 + .385 (70)			3.63 + .632 (70)	+	C	7.54 + .980 (59)		A
WEEK 18	5.08 + .447 (75)	4.39 + .403 (70)		A	2.79 + .895 (70)	*	C	6.49 + 1.05 (59)		B
WEEK 19	5.71 + .399 (75)	6.81 + .381 (70)	*	A	5.70 + .674 (70)			3.89 + 1.30 (57)		B
WEEK 20	5.91 + .354 (75)	5.23 + .439 (70)		A	4.24 + .679 (70)	*	B	7.23 + 1.32 (52)		B
WEEK 21	5.04 + .370 (75)	3.93 + .441 (70)		B	2.47 + .723 (70)	+	D	3.64 + .997 (50)		B
WEEK 22	3.96 + .436 (75)	5.40 + .306 (70)	+	C	3.56 + .702 (70)		A	3.44 + 1.15 (48)		A
WEEK 23	1.00 + .543 (75)	-0.63 + .472 (70)	*	D	-1.57 + .700 (70)	+	D	0.45 + 1.52 (47)		D
WEEK 24	4.48 + .514 (75)	5.51 + .489 (70)		B	3.89 + .941 (70)		A	1.93 + 1.49 (43)		D

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
T = TREATMENT-CONTROL CONTRAST ;
R = TREATMENT-CONTROL RATIO TEST : UPPER CONFIDENCE LEVEL LOWER THAN CONTROL MEAN BY AT LEAST 10 PERCENT - A, 20 PERCENT - B, 35 PERCENT - C, 50 PERCENT -D. RATIO TEST CANNOT BE CALCULATED - X.
† DOSE LEVEL REDUCED TO 100 MG/KG/DAY STARTING WITH WEEK 13.

APPENDIX J (CONTINUED)

DEPENDENT VARIABLE	CONTROL GROUP	TREATMENT GROUPS 12.5 MG/KG	T	R	50 MG/KG	T	R	100 MG/KG †	T	R
WEEK 25	4.11 ± .451 (75)	4.90 ± .396 (70)		A	6.19 ± .743 (70)	*	D	3.73 ± 1.99 (37)		
WEEK 26	5.25 ± .409 (75)	4.97 ± .425 (70)			1.99 ± .839 (70)	+	D	4.06 ± 1.48 (34)		B
WEEK 27	1.00 ± .424 (75)	0.63 ± .423 (70)		C	2.84 ± .739 (70)	*	D	-0.30 ± 1.29 (30)		D
WEEK 28	4.19 ± .417 (75)	5.33 ± .431 (70)		B	4.20 ± .812 (70)			1.74 ± 2.14 (27)		D
WEEK 29	5.43 ± .435 (75)	4.71 ± .476 (70)		A	2.04 ± 1.20 (70)	+	D	8.28 ± 1.64 (25)		D
WEEK 30	3.04 ± .385 (75)	3.40 ± .441 (70)		A	2.09 ± .758 (70)		B	1.63 ± 1.64 (24)		C
WEEK 31	1.56 ± .418 (75)	2.59 ± .360 (70)		D	0.70 ± .974 (70)		D	3.00 ± 1.77 (23)		D
WEEK 32	3.03 ± .486 (75)	1.47 ± .431 (70)	*	D	0.97 ± .802 (70)	*	D	-2.48 ± 4.84 (21)		D
WEEK 33	4.45 ± .393 (75)	2.94 ± .369 (70)	+	B	2.19 ± .689 (70)	+	D	3.47 ± 1.41 (19)		B
WEEK 34	5.08 ± .481 (75)	4.31 ± .535 (70)		A	2.16 ± .732 (69)	+	D			
WEEK 35	2.81 ± .446 (75)	2.84 ± .465 (70)			-0.68 ± 1.01 (69)	+	D			
WEEK 36	3.95 ± .480 (75)	2.96 ± .400 (70)		B	1.23 ± .905 (69)	+	D			

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
T = TREATMENT-CONTROL CONTRAST ;
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 PERCENT - A, 20 PERCENT - B, 35 PERCENT - C, 50 PERCENT - D. RATIO TEST CANNOT BE CALCULATED - X .
† HIGH DOSE TERMINATED AFTER 33 WEEKS ON TEST.

DEPENDENT VARIABLE	TREATMENT GROUPS: CONTROL GROUP	12.5 MG/KG	T	R	50 MG/KG	T	R
WEEK 37	4.01 + .469 (75)	1.34 + .400 (70)	+	D	-2.90 + 1.71 (67)	+	D
WEEK 38	4.48 + .425 (75)	4.40 + .451 (70)			2.55 + 1.51 (66)		C
WEEK 39	1.21 + .410 (75)	1.40 + .471 (70)		A	0.18 + 1.07 (66)		D
WEEK 40	0.92 + .446 (75)	1.40 + .519 (70)		D	5.26 + 1.05 (65)	+	D
WEEK 41	3.49 + .451 (75)	3.20 + .422 (70)			0.26 + 1.19 (65)	*	D
WEEK 42	1.68 + .465 (75)	1.43 + .377 (70)		A	-0.66 + 1.11 (64)		D
WEEK 43	1.13 + .455 (75)	1.47 + .438 (70)		B	4.08 + 1.19 (64)	*	D
WEEK 44	4.09 + .552 (75)	5.36 + .454 (70)		B	4.84 + 1.07 (64)		A
WEEK 45	3.09 + .401 (75)	3.23 + .640 (70)			3.45 + 1.02 (64)		A
WEEK 46	-1.25 + .440 (75)	-1.59 + .392 (70)		B	0.82 + .965 (61)		D
WEEK 47	4.77 + .442 (74)	2.56 + .510 (70)	+	C	1.21 + .921 (61)	+	D
WEEK 48	1.05 + .425 (74)	1.40 + .469 (70)		B	-0.95 + .958 (59)		D

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARNETHESES
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ;
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST
10 PERCENT - A, 20 PERCENT - B, 35 PERCENT - C, 50 PERCENT - D. RATIO TEST CANNOT BE CALCULATED - X.

APPENDIX J (CONTINUED)

DEPENDENT VARIABLE	CONTROL GROUP	TREATMENT GROUPS 12.5 MG/KG	T	R	50 MG/KG	T	R
WEEK 49	-2.05 + .431 (74)	-1.14 + .413 (70)		C	-0.64 + .966 (59)		D
WEEK 50	2.97 + .444 (74)	1.76 + 1.11 (70)		C	1.47 + 1.05 (58)		D
WEEK 51	2.76 + .434 (74)	4.10 + .926 (70)		C	2.25 + .994 (57)		A
WEEK 52	-1.99 + .644 (74)	-2.31 + .645 (70)		A	-0.67 + .995 (57)		D
WEEK 53	3.06 + .934 (64)	5.03 + .505 (60)		D	3.84 + 1.15 (49)		B
WEEK 54	1.63 + .741 (64)	-0.85 + .515 (60)	+	D	-2.49 + .889 (49)	+	D
WEEK 55	-1.56 + .867 (64)	1.35 + .749 (60)	*	D	2.60 + 1.41 (47)	*	D
WEEK 56	-3.70 + .858 (64)	-5.47 + .633 (60)		C	-3.49 + 1.32 (45)		
WEEK 57	3.53 + .641 (64)	3.55 + .530 (60)			3.64 + .999 (45)		
WEEK 58	2.17 + .586 (64)	0.98 + .468 (60)		D	0.39 + 1.13 (44)		D
WEEK 59	2.30 + .458 (64)	3.43 + .490 (60)		C	3.24 + 1.31 (42)		C
WEEK 60	-0.05 + .405 (64)	0.80 + .474 (60)		D	-2.51 + 1.10 (41)	*	D

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ;
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEANS BY AT LEAST 10 PERCENT - A, 20 PERCENT - B, 35 PERCENT - C, 50 PERCENT - D. RATIO TEST CANNOT BE CALCULATED - X.

DEPENDENT VARIABLE	CONTROL GROUP	TREATMENT GROUPS: 12.5 MG/KG	T	R	TREATMENT GROUPS: 50 MG/KG	T	R
WEEK 61	4.20 ± .535 (64)	1.28 ± 1.77 (60)		D	0.83 ± .887 (41)	+	D
WEEK 62	-0.52 ± .709 (64)	-0.18 ± .485 (60)		D	-0.27 ± 1.46 (41)		C
WEEK 63	4.14 ± .535 (64)	1.80 ± .589 (60)	+	D	0.03 ± 1.70 (39)	*	D
WEEK 64	1.29 ± .720 (63)	0.28 ± .504 (60)		D	-2.23 ± .956 (39)	+	D
WEEK 65	-3.50 ± .946 (62)	-1.92 ± .690 (60)		C	0.31 ± 1.83 (39)		D
WEEK 66	4.74 ± .969 (62)	2.77 ± .529 (60)		C	1.79 ± .927 (39)	*	D
WEEK 67	-1.52 ± .532 (61)	0.58 ± .527 (60)	+	D	1.92 ± 1.47 (39)	*	D
WEEK 68	-1.43 ± .489 (61)	-1.15 ± .429 (60)		A	-0.18 ± 1.29 (39)		D
WEEK 69	1.08 ± .508 (61)	0.50 ± .487 (60)		D	2.23 ± 1.25 (39)		D
WEEK 70	0.32 ± .527 (60)	-0.87 ± .460 (60)		D	0.61 ± 1.40 (38)		D
WEEK 71	3.52 ± .571 (60)	2.52 ± .400 (60)		B	-1.37 ± 2.10 (38)	*	D
WEEK 72	0.87 ± .457 (60)	-0.60 ± .457 (60)	*	D	1.25 ± 1.35 (36)		C

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
T = TREATMENT-CONTROL CONTRAST;
R = TREATMENT-CONTROL RATIO TEST : UPPER CONFIDENCE LEVEL LOWER THAN CONTROL MEAN BY AT LEAST
10 PERCENT - A, 20 PERCENT - B, 35 PERCENT - C, 50 PERCENT - D. RATIO TEST CANNOT BE CALCULATED - X.

APPENDIX J (CONTINUED)

DEPENDENT VARIABLE	CONTROL GROUP	TREATMENT GROUPS: 12.5 MG/KG	T	R	TREATMENT GROUPS: 50 MG/KG	T	R
WEEK 73	0.27 + .577 (60)	0.15 + .517 (60)		C	-3.00 + 2.26 (31)		D
WEEK 74	-0.63 + 1.25 (60)	0.30 + .537 (60)		D	0.13 + 1.58 (31)		D
WEEK 75	1.62 + .935 (60)	-1.17 + .522 (60)	*	D	-1.45 + 2.40 (29)		D
WEEK 76	-0.60 + .415 (60)	-0.60 + .576 (60)			1.76 + .924 (29)	*	D
WEEK 77	0.35 + .521 (60)	-0.32 + .670 (60)		D	0.43 + 1.74 (28)		B
WEEK 78	0.68 + .516 (60)	0.93 + .540 (59)		C	0.81 + 2.15 (27)		A
WEEK 79	-2.38 + 1.20 (60)	-0.24 + .535 (59)		D	-0.36 + 2.01 (25)		D
WEEK 80	0.33 + 1.02 (60)	-2.24 + 1.26 (59)		D	2.08 + 2.13 (25)		D
WEEK 81	1.32 + .572 (59)	1.14 + 1.28 (59)		A	-0.12 + 1.14 (25)		D
WEEK 82	-2.10 + .507 (59)	-2.34 + .817 (59)		A	0.92 + 1.22 (24)	*	D
WEEK 83	0.19 + .498 (59)	0.14 + .831 (58)		B	0.29 + 1.18 (24)		D
WEEK 84	-1.46 + .838 (59)	-2.31 + .929 (58)		D	-0.58 + 1.27 (24)		D

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
T = TREATMENT-CONTROL CONTRAST ;
R = TREATMENT-CONTROL RATIO TEST : UPPER CONFIDENCE LEVEL LOWER THAN CONTROL MEAN BY AT LEAST
10 PERCENT - A, 20 PERCENT - B, 35 PERCENT - C, 50 PERCENT - D. RATIO TEST CANNOT BE CALCULATED - X.

DEPENDENT VARIABLE	CONTROL GROUP	TREATMENT GROUPS			
		12.5 MG/KG	T R	50 MG/KG	T R
WEEK 85	1.31 + .562 (59)	-0.12 + .722 (58)	D	-0.23 + 1.40 (22)	D
WEEK 86	-0.42 + .667 (59)	-3.62 + 1.30 (58)	* D	-1.18 + 1.09 (22)	D
WEEK 87	-0.25 + .744 (59)	1.89 + 1.09 (57)	D	1.64 + 1.78 (22)	D
WEEK 88	-1.31 + .803 (59)	-0.51 + .581 (57)	D	-0.19 + .925 (21)	D
WEEK 89	-7.29 + 2.09 (59)	-4.35 + .683 (57)	C	-3.95 + 1.33 (19)	C
WEEK 90	2.23 + 1.27 (57)	-0.75 + .670 (57)	* D	1.42 + 1.74 (19)	C
WEEK 91	-0.23 + 1.14 (57)	0.88 + .639 (57)	D	-1.79 + 1.93 (19)	D
WEEK 92	-4.64 + .662 (56)	-5.61 + .500 (57)	B	-4.79 + 1.45 (19)	
WEEK 93	4.29 + .657 (56)	3.84 + .479 (57)	A	4.74 + 1.50 (19)	A
WEEK 94	-1.86 + 1.19 (56)	-1.86 + .594 (57)		-0.42 + 1.40 (19)	D
WEEK 95	-0.64 + .998 (55)	-1.79 + .894 (57)	D	-2.16 + 1.61 (19)	D
WEEK 96	-2.33 + .816 (54)	-1.20 + .625 (56)	C	-0.32 + 1.74 (19)	D

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
T = TREATMENT-CONTROL CONTRAST ;
R = TREATMENT-CONTROL RATIO TEST : UPPER CONFIDENCE LEVEL LOWER THAN CONTROL MEAN BY AT LEAST 10 PERCENT - A, 20 PERCENT - B, 35 PERCENT - C, 50 PERCENT - D. RATIO TEST CANNOT BE CALCULATED - X.

APPENDIX J (CONCLUDED)

DEPENDENT VARIABLE	CONTROL GROUP	TREATMENT GROUPS			
		12.5 MG/KG	T R	50 MG/KG	T R
WEEK 97	-1.53 + .850 (53)	-1.55 + .704 (55)		-3.22 + 3.16 (18)	X
WEEK 98	1.10 + .719 (52)	-0.29 + 1.34 (55)	D	-2.75 + 2.77 (16)	X
WEEK 99	-4.35 + .678 (52)	-5.04 + 1.07 (55)	A	-1.88 + 2.36 (16)	X
WEEK 100	-5.86 + .906 (51)	-5.31 + .671 (54)		-2.13 + 2.02 (16)	D
WEEK 101	-0.65 + .803 (49)	-0.74 + 1.14 (53)	A	-1.50 + 1.64 (16)	D
WEEK 102	-7.09 + .878 (47)	-5.73 + .676 (49)	A	-5.79 + 3.30 (14)	X
WEEK 103	-4.06 + .974 (47)	-4.10 + .870 (49)		-1.38 + 2.36 (13)	D
WEEK 104	-1.30 + 1.13 (47)	-3.02 + .978 (49)	D	-7.31 + 1.89 (13)	+ D

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
T = TREATMENT-CONTROL CONTRAST;
R = TREATMENT-CONTROL RATIO TEST : UPPER CONFIDENCE LEVEL LOWER THAN CONTROL MEAN BY AT LEAST 10 PERCENT - A, 20 PERCENT - B, 35 PERCENT - C, 50 PERCENT - D. RATIO TEST CANNOT BE CALCULATED - X.

APPENDIX K

AVERAGE WEEKLY BODY WEIGHT GAIN (G) OF FEMALE RATS
TREATED WITH NAP

DEPENDENT VARIABLE	CONTROL GROUP	TREATMENT GROUPS					
		12.5 MG/KG	T R	50 MG/KG	T R	200 MG/KG	T R
WEEK 1	10.91 + .989 (75)	15.56 + .397 (70)	+ C	10.50 + .620 (70)		-7.04 + .541 (70)	+ D
WEEK 2	15.12 + 1.28 (75)	7.69 + .989 (70)	+ C	7.81 + .997 (70)	+ C	8.30 + .722 (70)	+ C
WEEK 3	13.63 + .952 (75)	15.03 + .823 (70)	A	14.34 + .795 (70)		8.60 + .410 (70)	+ C
WEEK 4	10.24 + .599 (75)	9.59 + .313 (70)		6.71 + .415 (70)	+ B	7.87 + .374 (70)	+ B
WEEK 5	8.68 + .360 (75)	7.46 + .322 (70)	* A	7.04 + .392 (70)	+ A	7.40 + .361 (70)	* A
WEEK 6	5.80 + .363 (75)	5.56 + .261 (70)		4.66 + .288 (70)	* A	5.11 + .318 (70)	
WEEK 7	3.66 + .316 (74)	6.19 + .334 (70)	+ D	5.17 + .326 (70)	+ C	5.86 + .317 (70)	+ D
WEEK 8	6.99 + .253 (74)	3.67 + .248 (70)	+ C	2.20 + .299 (70)	+ D	4.81 + .364 (70)	+ B
WEEK 9	5.54 + .282 (74)	3.09 + .310 (70)	+ C	3.47 + .287 (70)	+ C	6.09 + .431 (70)	
WEEK 10	3.46 + .306 (74)	4.64 + .262 (70)	+ B	4.14 + .302 (70)	A	6.23 + .388 (70)	+ D
WEEK 11	3.20 + .317 (74)	1.46 + .308 (70)	+ D	2.06 + .277 (70)	+ C	6.17 + .351 (69)	+ D
WEEK 12	1.85 + .321 (74)	2.70 + .267 (70)	* C	1.39 + .243 (70)	B	4.96 + .538 (69)	+ D

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ;
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST
10 PERCENT - A, 20 PERCENT - B, 35 PERCENT - C, 50 PERCENT - D. RATIO TEST CANNOT BE CALCULATED - X .

APPENDIX K (CONTINUED)

DEPENDENT VARIABLE	CONTROL GROUP	TREATMENT GROUPS 12.5 MG/KG	T	R	50 MG/KG	T	R	100 MG/KG †	T	R
WEEK 13	3.81 + .329 (74)	2.77 + .294 (70)	*	B	4.70 + .247 (70)	*	B	9.03 + .544 (69)	+	D
WEEK 14	2.55 + .355 (74)	2.26 + .288 (70)		A	1.00 + .343 (70)	+	D	5.10 + .594 (69)	+	D
WEEK 15	1.42 + .369 (74)	2.44 + .302 (70)	*	D	0.54 + .309 (70)		D	7.61 + .491 (69)	+	D
WEEK 16	1.69 + .418 (74)	0.44 + .299 (70)	*	D	2.97 + .287 (70)	*	D	2.64 + .505 (69)		D
WEEK 17	2.70 + .409 (74)	2.26 + .297 (70)		A	1.67 + .300 (70)	*	C	3.51 + .450 (69)		B
WEEK 18	0.70 + .381 (74)	-0.66 + .315 (70)	+	D	0.20 + .375 (70)		D	5.17 + .652 (69)	+	D
WEEK 19	2.47 + .434 (74)	4.30 + .269 (70)	+	D	2.17 + .326 (70)		A	3.12 + .669 (69)		B
WEEK 20	2.20 + .391 (74)	1.86 + .326 (70)		A	2.27 + .358 (70)			6.71 + .592 (69)	+	D
WEEK 21	1.59 + .372 (74)	1.33 + .348 (70)		A	-1.10 + .393 (70)	+	D	1.65 + .607 (69)		
WEEK 22	0.88 + .381 (74)	0.91 + .364 (70)			1.77 + .307 (70)		D	4.28 + .596 (69)	+	D
WEEK 23	-0.64 + .434 (74)	-1.04 + .397 (70)		D	0.33 + .383 (70)		D	1.59 + .634 (69)	+	D
WEEK 24	0.64 + .377 (74)	1.51 + .316 (70)		D	1.79 + .327 (70)	*	D	4.58 + .570 (69)	+	D

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
T = TREATMENT-CONTROL CONTRAST ;
R = TREATMENT-CONTROL RATIO TEST : UPPER CONFIDENCE LEVEL LOWER THAN CONTROL MEAN BY AT LEAST 10 PERCENT - A, 20 PERCENT - B, 35 PERCENT - C, 50 PERCENT -D. RATIO TEST CANNOT BE CALCULATED - X.
† DOSE LEVEL REDUCED TO 100 MG/KG/DAY STARTING WITH WEEK 13.

APPENDIX K (CONTINUED)

DEPENDENT VARIABLE	CONTROL GROUP	TREATMENT GROUPS 12.5 MG/KG	T	R	50 MG/KG	T	R	100 MG/KG †	T	R
WEEK 25	1.69 ± .438 (74)	-1.13 ± .713 (70)	+	D	0.74 ± .371 (70)		D	3.45 ± .520 (69)	*	D
WEEK 26	1.43 ± .375 (74)	2.97 ± .552 (70)	*	D	1.46 ± .325 (70)			3.41 ± .714 (69)	*	D
WEEK 27	-0.27 ± .341 (74)	-0.77 ± .353 (70)		D	0.40 ± .385 (70)		D	1.55 ± .614 (69)	*	D
WEEK 28	1.69 ± .360 (74)	2.61 ± .398 (70)		D	1.51 ± .347 (70)		A	3.46 ± .649 (69)	*	D
WEEK 29	2.66 ± .370 (74)	1.80 ± .263 (70)		B	1.69 ± .475 (70)		C	2.91 ± .662 (69)		
WEEK 30	1.92 ± .363 (74)	1.90 ± .301 (70)			2.16 ± .422 (70)		A	0.14 ± .600 (69)	*	D
WEEK 31	1.69 ± .364 (74)	0.51 ± .274 (70)	*	D	0.30 ± .484 (70)	*	D	1.59 ± .475 (69)		
WEEK 32	0.70 ± .339 (74)	-0.24 ± .297 (70)	*	D	-0.83 ± .506 (70)	*	D	0.86 ± .611 (69)		B
WEEK 33	1.77 ± .337 (74)	1.24 ± .356 (70)		B	0.37 ± .586 (70)	*	D	1.16 ± .616 (69)		B
WEEK 34	3.11 ± .373 (74)	2.01 ± .377 (70)	*	C	3.09 ± .498 (70)					
WEEK 35	1.82 ± .331 (74)	2.96 ± .285 (70)	+	D	2.70 ± .577 (70)		C			
WEEK 36	1.27 ± .377 (74)	0.10 ± .307 (70)	*	D	1.60 ± .506 (70)		B			

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
T = TREATMENT-CONTROL CONTRAST ;
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVALS GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 PERCENT - A, 20 PERCENT - B, 35 PERCENT - C, 50 PERCENT - D. RATIO TEST CANNOT BE CALCULATED - X .
† HIGH DOSE TERMINATED AFTER 33 WEEKS ON TEST.

APPENDIX K (CONTINUED)

DEPENDENT VARIABLE	CONTROL GROUP	TREATMENT GROUPS 12.5 MG/KG	T	R	50 MG/KG	T	R
WEEK 37	2.14 + .370 (74)	0.03 + .329 (70)	+	D	0.34 + .521 (70)	+	D
WEEK 38	3.32 + .415 (74)	3.84 + .413 (70)		A	3.74 + .463 (70)		A
WEEK 39	0.51 + .416 (74)	0.33 + .388 (70)		C	0.93 + .538 (70)		D
WEEK 40	0.50 + .375 (74)	-1.19 + .297 (70)	+	D	1.20 + .601 (70)		D
WEEK 41	2.15 + .360 (74)	1.87 + .278 (70)		A	2.31 + .561 (70)		
WEEK 42	0.58 + .483 (74)	0.13 + .328 (70)		D	1.24 + .543 (70)		D
WEEK 43	1.20 + .411 (74)	1.00 + .298 (70)		A	-0.56 + .685 (70)	*	D
WEEK 44	1.61 + .399 (74)	1.09 + .301 (70)		B	2.37 + .601 (70)		C
WEEK 45	2.22 + .352 (74)	2.93 + .322 (70)		B	3.47 + .403 (70)	*	D
WEEK 46	0.35 + .452 (74)	-1.09 + .359 (70)	*	D	-0.10 + .518 (70)		D
WEEK 47	1.78 + .471 (74)	1.76 + .368 (70)			-0.39 + .601 (70)	+	D
WEEK 48	2.12 + .462 (74)	0.00 + .381 (69)	+	D	1.37 + .613 (70)		C

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARNETHESES
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ;
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEAN BY AT LEAST 10 PERCENT - A, 20 PERCENT - B, 35 PERCENT - C, 50 PERCENT - D. RATIO TEST CANNOT BE CALCULATED - X.

DEPENDENT VARIABLE	CONTROL GROUP	TREATMENT GROUPS 12.5 MG/KG	T	R	50 MG/KG	T	R
WEEK 49	-1.16 + .378 (74)	-0.54 + .371 (69)		D	-1.07 + .927 (70)		
WEEK 50	2.09 + .348 (74)	3.07 + .367 (69)		C	6.06 + .984 (70)	+	D
WEEK 51	2.65 + .415 (74)	0.97 + .347 (69)	+	D	1.63 + .632 (70)		C
WEEK 52	-1.14 + .424 (74)	-1.32 + .444 (69)		A	-0.97 + .606 (70)		A
WEEK 53	4.66 + .506 (64)	4.00 + .391 (59)		A	4.62 + .761 (60)		
WEEK 54	1.44 + .479 (64)	-0.22 + .422 (59)	*	D	-0.98 + .846 (60)	*	D
WEEK 55	2.05 + .523 (64)	2.42 + .509 (59)		A	2.68 + .684 (60)		B
WEEK 56	-0.40 + .504 (63)	-1.22 + .491 (59)		D	-0.12 + .609 (60)		D
WEEK 57	2.22 + .417 (63)	1.32 + .537 (59)		C	0.43 + .661 (60)	*	D
WEEK 58	0.92 + .429 (63)	-1.98 + .469 (59)	+	D	0.50 + .670 (60)		C
WEEK 59	2.33 + .466 (63)	2.44 + .583 (59)			3.90 + .610 (60)	*	D
WEEK 60	1.83 + .507 (63)	1.17 + .617 (59)		C	0.62 + .727 (60)		D

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
BC = BARTLETTS CHI-SQUARE ; T = TREATMENT-CONTROL CONTRAST ;
R = TREATMENT-CONTROL RATIO TEST : CONFIDENCE INTERVAL GREATER OR LOWER THAN CONTROL MEANS BY AT LEAST 10 PERCENT - A, 20 PERCENT - B, 35 PERCENT - C, 50 PERCENT - D. RATIO TEST CANNOT BE CALCULATED - X.

APPENDIX K (CONTINUED)

DEPENDENT VARIABLE	CONTROL GROUP	TREATMENT GROUPS				
		12.5 MG/KG	T	R	50 MG/KG	T R
WEEK 61	6.67 + .561 (63)	2.78 + .551 (59)	+	D	2.02 + .756 (60)	+ D
WEEK 62	1.29 + .601 (63)	0.66 + .520 (59)		C	1.97 + .676 (60)	D
WEEK 63	2.97 + .510 (63)	4.15 + .470 (59)		C	1.07 + .734 (60)	* D
WEEK 64	2.73 + .441 (63)	0.97 + .575 (59)	*	D	1.35 + .632 (60)	D
WEEK 65	0.89 + .567 (63)	0.59 + .503 (58)		B	-3.03 + 1.01 (60)	+ D
WEEK 66	2.68 + .539 (63)	2.66 + .615 (58)			3.18 + 1.01 (60)	A
WEEK 67	1.89 + .533 (63)	2.55 + .492 (58)		C	0.93 + .885 (60)	D
WEEK 68	-1.70 + 1.02 (63)	0.10 + .453 (58)		D	1.78 + .755 (60)	+ D
WEEK 69	4.68 + .818 (63)	3.12 + .492 (58)		B	2.88 + .879 (60)	C
WEEK 70	1.90 + .546 (63)	0.29 + .456 (58)	*	D	-1.50 + .780 (58)	+ D
WEEK 71	3.59 + .503 (63)	2.76 + .423 (58)		B	1.31 + .793 (58)	* D
WEEK 72	1.44 + .736 (63)	2.12 + .476 (58)		C	1.16 + .715 (58)	B

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
T = TREATMENT-CONTROL CONTRAST;
R = TREATMENT-CONTROL RATIO TEST : UPPER CONFIDENCE LEVEL LOWER THAN CONTROL MEAN BY AT LEAST 10 PERCENT - A, 20 PERCENT - B, 35 PERCENT - C, 50 PERCENT - D. RATIO TEST CANNOT BE CALCULATED - X.

APPENDIX K (CONTINUED)

DEPENDENT VARIABLE	TREATMENT GROUPS: CONTROL GROUP	12.5 MG/KG	T	R	50 MG/KG	T	R
WEEK 73	1.85 + .488 (61)	1.83 + .527 (58)			-0.84 + .757 (58)	+	D
WEEK 74	0.46 + .498 (61)	1.38 + .403 (58)		D	2.62 + .774 (58)	*	D
WEEK 75	1.44 + .590 (61)	0.22 + .482 (58)		D	-2.53 + 1.04 (58)	+	D
WEEK 76	0.52 + .553 (61)	2.26 + .537 (58)	*	D	3.22 + .863 (58)	+	D
WEEK 77	2.66 + 1.68 (61)	0.79 + .507 (57)		D	0.26 + .788 (58)		D
WEEK 78	2.43 + .598 (61)	2.11 + .547 (57)		A	1.48 + .804 (58)		C
WEEK 79	-0.60 + 1.71 (60)	0.75 + .482 (57)		D	-0.69 + .769 (58)		A
WEEK 80	2.32 + .767 (60)	2.54 + .749 (57)			2.28 + .852 (58)		
WEEK 81	1.87 + .609 (60)	1.42 + .633 (57)		B	0.32 + .751 (57)		D
WEEK 82	0.92 + .558 (60)	1.19 + .598 (57)		B	-0.89 + .867 (57)		D
WEEK 83	2.95 + .542 (60)	2.48 + .826 (56)		A	1.48 + .747 (56)		C
WEEK 84	0.93 + .485 (60)	0.67 + .547 (55)		B	-2.39 + .836 (56)	+	D

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
T = TREATMENT-CONTROL CONTRAST ;
R = TREATMENT-CONTROL RATIO TEST : UPPER CONFIDENCE LEVEL LOWER THAN CONTROL MEAN BY AT LEAST
10 PERCENT - A, 20 PERCENT - B, 35 PERCENT - C, 50 PERCENT - D. RATIO TEST CANNOT BE CALCULATED - X.

APPENDIX K (CONTINUED)

DEPENDENT VARIABLE	CONTROL GROUP	TREATMENT GROUPS 12.5 MG/KG	T	R	50 MG/KG	T	R
WEEK 85	1.88 + .622 (60)	0.09 + .536 (55)	*	D	2.71 + .814 (56)		C
WEEK 86	-1.05 + .615 (60)	0.64 + .484 (55)	*	D	-1.59 + .835 (56)		D
WEEK 87	0.39 + .840 (59)	2.05 + .548 (55)		D	0.84 + .831 (56)		D
WEEK 88	1.34 + .630 (59)	0.93 + .461 (54)		B	0.95 + .744 (56)		B
WEEK 89	-0.05 + .658 (59)	-3.11 + .715 (54)	+	D	-1.51 + .936 (55)		D
WEEK 90	-0.75 + .531 (59)	-0.80 + .605 (54)			1.63 + 1.09 (54)		D
WEEK 91	1.95 + .545 (59)	1.30 + .680 (54)		B	1.04 + .917 (52)		C
WEEK 92	-2.17 + .708 (59)	-0.91 + .568 (54)		D	0.98 + .766 (52)	+	D
WEEK 93	3.54 + .769 (59)	1.58 + .754 (53)		D	0.56 + .903 (52)	+	D
WEEK 94	-1.97 + .886 (59)	1.26 + .544 (53)	+	D	0.45 + .726 (51)	*	D
WEEK 95	-0.53 + .605 (58)	-0.90 + 1.15 (52)		D	-1.43 + 1.43 (51)		D
WEEK 96	0.65 + .688 (57)	0.96 + .628 (47)		C	3.39 + 1.22 (51)		D

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
T = TREATMENT-CONTROL CONTRAST ;
R = TREATMENT-CONTROL RATIO TEST : UPPER CONFIDENCE LEVEL LOWER THAN CONTROL MEAN BY AT LEAST 10 PERCENT - A, 20 PERCENT - B, 35 PERCENT - C, 50 PERCENT - D. RATIO TEST CANNOT BE CALCULATED - X.

APPENDIX K (CONCLUDED)

DEPENDENT VARIABLE	CONTROL GROUP	TREATMENT GROUPS: 12.5 MG/KG	T	R	TREATMENT GROUPS: 50 MG/KG	T	R
WEEK 97	-0.61 + .624 (56)	-0.41 + .658 (46)		B	-1.43 + .798 (51)		D
WEEK 98	1.65 + 1.03 (55)	1.96 + 1.06 (46)		A	1.58 + .891 (50)		
WEEK 99	-2.63 + .768 (54)	-0.78 + .594 (45)		D	-3.40 + 1.65 (50)		B
WEEK 100	-2.70 + .580 (53)	-2.86 + .643 (44)			1.00 + 1.53 (50)	*	D
WEEK 101	0.98 + .637 (51)	1.66 + .594 (44)		D	0.27 + .928 (49)		D
WEEK 102	-4.82 + .733 (50)	-1.70 + .780 (43)	+	D	-0.67 + .843 (49)	+	D
WEEK 103	-0.80 + .753 (49)	-0.84 + .800 (43)			-2.04 + .802 (47)		D
WEEK 104	-0.51 + .734 (49)	-1.62 + .672 (42)		D	0.40 + .962 (47)		D

ENTRIES ARE MEANS AND STANDARD ERRORS WITH GROUP N IN PARENTHESES
* CONFIDENCE LEVEL = .95
+ CONFIDENCE LEVEL = .99
T = TREATMENT-CONTROL CONTRAST;
R = TREATMENT-CONTROL RATIO TEST : UPPER CONFIDENCE LEVEL LOWER THAN CONTROL MEAN BY AT LEAST 10 PERCENT - A, 20 PERCENT - B, 35 PERCENT - C, 50 PERCENT - D. RATIO TEST CANNOT BE CALCULATED - X.

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Feb.

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